

**Studies Towards the Synthesis of Nano-Diamondoid
Hydrocarbon Cyclohexamantane**

A thesis submitted by

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Abstract

Adamantane ($C_{10}H_{16}$) is the smallest unit cage structure of the diamond crystal lattice. Other diamondoid hydrocarbons are also known, such as diamantane and triamantane. In 2003, the isolation and structural elucidation of a highly symmetrical and remarkably stable “natural product” cyclohexamantane ($C_{26}H_{30}$) was reported.¹ The structure of the nanometer-sized hydrocarbon cyclohexamantane was shown by X-ray crystallography to be the largest fully characterized fragment of the diamond lattice. Higher order diamondoid hydrocarbons may have great potential applications in pharmaceuticals, microelectronics and nanotechnology.²

Prior to von Schleyer's outstanding synthesis³, adamantane was a rare compound and only available in small quantities. The success to von Schleyer's synthesis was his appreciation of the fact that adamantane is the most stable hydrocarbon of formula $C_{10}H_{16}$. He used this knowledge to bring about the Lewis acid catalysed rearrangement (*via* a sequence of Wagner-Meerwein shifts) of a strained hydrogenated cyclopentadiene dimer ($C_{10}H_{16}$) to provide adamantane in high yield.

Our research goal is to prepare hydrocarbon precursors of formula $C_{26}H_{32}$ and to study their dehydrogenative rearrangements under acidic conditions as a concise synthetic route to cyclohexamantane ($C_{26}H_{30}$). Our investigations into two different approaches to build the rearrangement precursors ($C_{26}H_{32}$) are described in this thesis. In the first approach, a four-directional synthesis of the rearrangement precursor has been examined through **Route A** and **Route B**. A more concise approach *via* the Diels-Alder dimerisation of adamantanocyclopentadiene is also described herein.

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1. Dahl, J. E. P.; Moldowan, J. M.; Peakman, T. M.; Clardy, J. C.; Lobkovsky, E.; Olmstead, M. M.; May, P. W.; Davis, T. J.; Steeds, J. W.; Peters, K. E.; Pepper, A.; Ekuan, A.; Clarson, R. M. K. *Angew. Chem. Int. Ed.* **2003**, 42, 2040.
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Abbreviations

Å	Ångström
Ac	acetyl
AcOH	acetic acid
aq.	aqueous
Ar	aryl
Bn	benzyl
Boc	<i>tertiary</i> -butyl carbonyl
b.p.	boiling point
<i>br</i>	broad
Bu	butyl
<i>c</i>	concentration
°C	degrees Celsius
<i>ca.</i>	<i>circa</i>
cat.	catalytic
CI+	positive chemical ionisation
conc	concentrated
d	doublet
<i>d</i>	deuterated
dd	doublet of doublets
ddd	doublet of doublet of doublets
DCM	dichloromethane
DIBAL-H	di- <i>iso</i> -butylaluminium hydride
DMAP	4-dimethylaminopyridine
DME	dimethoxyethane
DMF	<i>N,N</i> -dimethylformamide
DMSO	dimethylsulfoxide
dt	doublet of triplets
dq	doublet of quartets
EI	electron impact

eq	equivalent(s)
Et	ethyl
g	gram(s)
GC-MS	gas chromatography-mass spectrometry
h	hour(s)
hex	hexane
HRMS	high resolution mass spectrometry
Hz	Hertz
<i>i</i>	<i>iso</i>
IBX	<i>o</i> -iodoxybenzoic acid
<i>i.e.</i>	<i>id est</i>
ImH	imidazole
IR	infra-red spectroscopy
<i>J</i>	coupling constant
KHMDS	potassium hexamethyldisilazide
L	litre
LDA	lithium di- <i>iso</i> -propylamide
LHMDS	lithium hexamethyldisilazide
LTMP	lithium 2,2,6,6-tetramethyl piperidine
m	multiplet
M	molar
<i>m</i>	<i>meta</i>
Me	methyl
mg	milligram(s)
MHz	megahertz
min	minute(s)
mL	millilitre(s)
μL	microlitres
mmol	millimole(s)
mol	mole(s)
m.p.	melting point

MPO	4-methoxypyridine- <i>N</i> -oxide
MS	mass spectrometry
NMR	nuclear magnetic resonance
<i>o</i>	<i>ortho</i>
<i>p</i>	<i>para</i>
pfb	perfluorobutyrate
Ph	phenyl
Piv	pivalyl
ppm	parts per million
Pr	propyl
q	quartet
quin	quintet
R	general substituent
r.t.	room temperature
s	singlet
sat.	saturated
t	triplet
td	triplet of doublets
<i>t</i> or <i>tert</i>	<i>tertiary</i>
TBAF	tetra- <i>n</i> -butylammonium fluoride
TBS	<i>tertiary</i> -butyldimethylsilyl
Tf	trifluoromethanesulfonyl (triflic)
tfa	trifluoroacetate
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
Ts	<i>para</i> -toluenesulfonyl (tosyl)
UV	ultraviolet
v	volume
W	Watts

w

weak

wt

weight

1. INTRODUCTION

1.1. Introduction to Diamondoid Hydrocarbons

1.1.1. Adamantane and Other Diamondoid Hydrocarbons

Nature has produced an astronomical number of natural products. Among them, thousands of intricate structures have fascinated organic chemists, and consequently have become the subject of many exquisite natural product syntheses. With rapidly developing organic synthetic methods and compound characterisation techniques, nowadays complex natural products can be synthesised in research laboratories. However, syntheses of some seemingly structurally basic but attractive hydrocarbons still remain unsolved. Among them are higher diamondoid hydrocarbons, such as cyclohexamantane (**1**) (Figure 1).

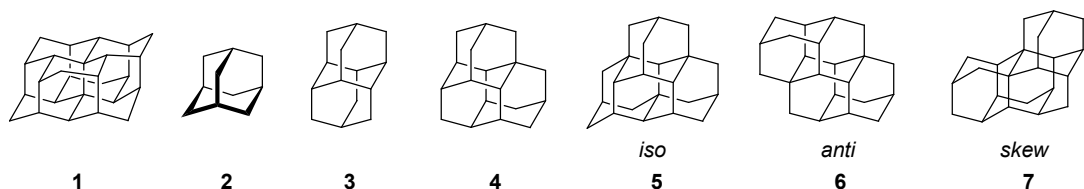


Figure 1. Structures of diamondoid hydrocarbons.

Diamondoids are “hydrocarbons that have a carbon framework that is superimposable on the diamond lattice”.¹ The simplest diamondoid hydrocarbon is adamantane (**2**) (Figure 1), whose name derives from “adamas”, the Greek word for diamond. Due to its unusual chemical and physical properties, adamantane (**2**) appealed to the chemical society as a *non-natural product* even before it was isolated from petroleum fractions by Landa in 1933.² The beautifully symmetrical structure was not confirmed until Prelog’s chemical synthesis of adamantane eight years later.³

In 1966, the second member of this family, diamantane (**3**) (Figure 1) was also found from petroleum sources.⁴ Accordingly, the third member of this diamondoid series is named triamantane (**4**) (Figure 1). At present scientists believe that diamondoids occur naturally in

all petroleum sources, albeit in very low concentrations (in the order of 1-100 ppm) and occur mostly as unsubstituted or alkyl-substituted adamantanes and diamantanes.⁵

Altogether, adamantane (**2**), diamantane (**3**) and triamantane (**4**) exist as single structural isomers and are regarded as lower diamondoids. Tetramantanes are higher diamondoids in this homologous series, and have three possible isomers *iso*-tetramantane (**5**), *anti*-tetramantane (**6**) and *skew*-tetramantane (**7**) (Figure 1). These correspond to the topological relationship of *iso*-butane, *anti*-butane and *skew*-butane of *n*-butane conformations.

1.1.2. Applications of Diamondoid Hydrocarbons

Scientists are interested in diamondoid hydrocarbons not only because of their structural intricacy and beauty, but also because of their wide applications in other research fields.

One example of medicinal chemistry applications is that 1-adamantyl amine hydrochloride is used extensively as an antidyskinetic to treat parkinsonism and related extrapyramidal syndromes and as a chemical antiviral agent to treat Type A influenza in humans.⁶ A virtue of the diamondoid hydrocarbon moiety is that it possesses high lipophilicity, but is not readily degraded in the human body, thus providing an ideal long-lasting platform for drug delivery. Another application in physical organic chemistry is that diamondoid hydrocarbons provide a perfect scaffold for carbocation and radical mechanistic studies, because of their rigid structures and lack of polarised heteroatom-carbon bonds.

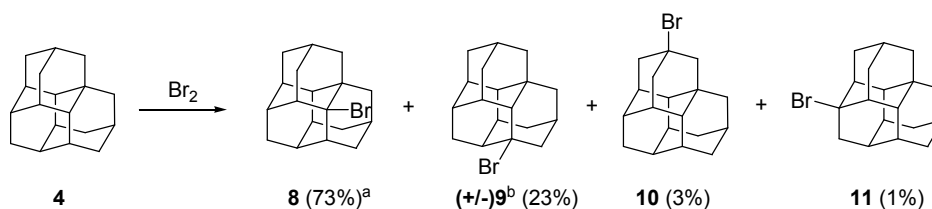
The applications of higher diamondoids are still in an early stage, due to their synthetic inaccessibility and the extremely low concentration of these compounds in natural source. From the point of view of material chemistry, higher diamondoid hydrocarbons starting from tetramantanes are in the category of organic nanostructures (1 to 2 nm). Such materials with controllable nanostructural characteristics have many potential applications in biotechnology and nanotechnology.⁷

Although it is believed that the worldwide crude petroleum supply is the only natural source of diamondoid hydrocarbons, the extremely low concentration, especially for the higher members of the family, means that few chemists are willing to tediously isolate milligram quantities of these diamondoids from the kilograms or even tons of petroleum necessary. Under these circumstances, a practical synthesis of these compounds would be very desirable. In **Section 1.2**, the history of diamondoid hydrocarbon syntheses will be reviewed and discussed.

1.1.3. Functionalisations of Diamondoid Hydrocarbons

Having briefly described the potential applications of diamondoid hydrocarbons in the fields of chemistry, physics and material sciences, a question still remains for synthetic organic chemists – how to selectively functionalise these hydrogen-terminated molecules to make them applicable to nanoscale manufacturing? The answer to this question was considered to be difficult because of the large number of similarly reactive C-H bonds. It is well established in the literature that reactions with electrophiles, radicals and strong single-electron oxidisers are the most practical methods for the functionalisations of cage hydrocarbon compounds.⁸ For example, reaction of triamantane (**4**) with neat bromine leads to a mixture of all possible tertiary bromo derivatives **8-11** (Scheme 1).⁹ Unfortunately, the more attractive apical 9-derivative **10** is only a minor isomer.

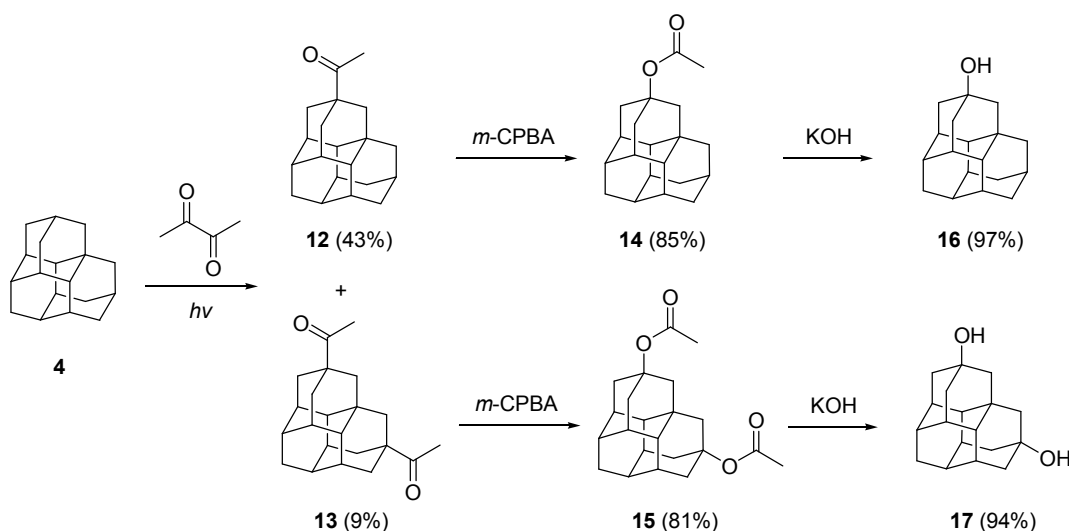
Scheme 1. Direct functionalisation of triamantane (**4**) from the previous literature.



^a % Product distribution; ^b For racemic compounds, only one enantiomer is shown.

Just recently, results from a collaboration between scientists in several different institutes have confirmed, both computationally and experimentally, that selective functionalisation of diamondoid hydrocarbons is possible.^{8,10,11,12} In the case of triamantane (**4**), selective preparation of the apical derivative was achieved by photo-oxidation with diacetyl (2,3-butanedione) as shown in Scheme 2. It was found that upon excitation, the triplet form of diacetyl preferentially abstracts a hydrogen from the least hindered apical position of triamantane (**4**) to give 9-acetyltriamantane (**12**) in high selectivity and good isolated yield.¹⁰ The second hydrogen abstraction also takes place predominantly at the next available apical position to yield 9,15-diacetyltriamantane (**13**). Ketones **12** and **13** are very useful synthetic intermediates to convert to other apical derivatives of triamantane (**4**). For example, 9-hydroxytriamantane (**16**) and 9,15-dihydroxytriamantane (**17**) can be obtained in excellent yields from ketones **12** and **13** respectively over a two-step procedure (Bayer-Villiger oxidation and the subsequent hydrolysis of esters to alcohols).

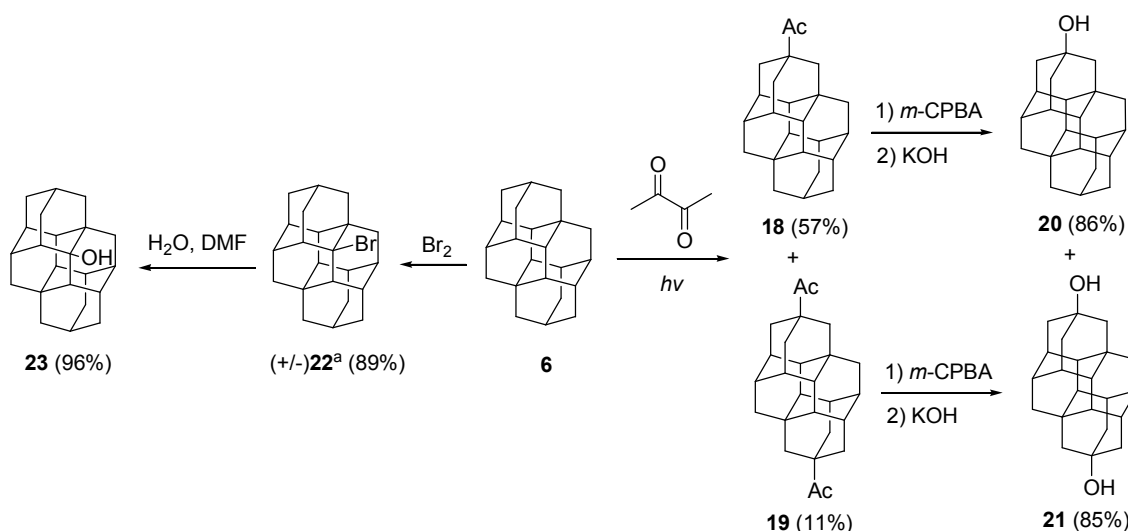
Scheme 2. Preparation of apical derivatives of triamantane (**4**) *via* photoacetylation.



The functionalisation of higher diamondoid hydrocarbon *anti*-tetramantane (**6**) had never been studied before these recent results. By using the same photoacetylation strategy as in the case of triamantane (**4**), selective preparation of apical hydroxyl derivatives **20** and **21** were obtained after a two-step reaction sequence (Scheme 3).¹⁰ Interestingly, the bromination of *anti*-tetramantane (**6**) gave 2-bromo-tetramantane (**22**) almost exclusively,

due to the exceptionally high stability of the corresponding 2-tetramantanyl cations. 2-Hydroxy-tetramantane (**23**) was synthesised in high yield after hydrolysis of **22** (Scheme 3).

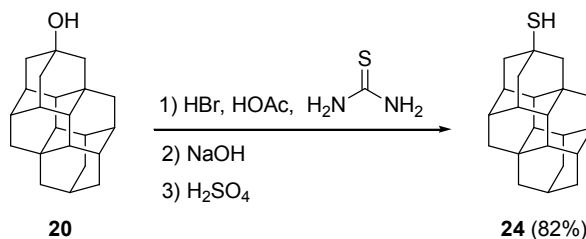
Scheme 3. Selective functionalisation of *anti*-tetramantane (**6**).



^a For racemic compounds, only one enantiomer is shown.

A convenient one-step procedure to prepare tertiary thiol compounds of diamondoid hydrocarbons has also been developed by treatment of hydroxyl-tetramantane **20** with thiourea in the presence of hydrobromic acid and acetic acid (Scheme 4).¹¹ Nano-diamondoids with incorporated SH groups, such as compound **24**, have great applications in molecular electronics, because the thiol groups can attach to noble metal surfaces to form self-assembled monolayers (SAMs).¹¹

Scheme 4. Preparation of tertiary thiol from hydroxyl-tetramantane **20**.

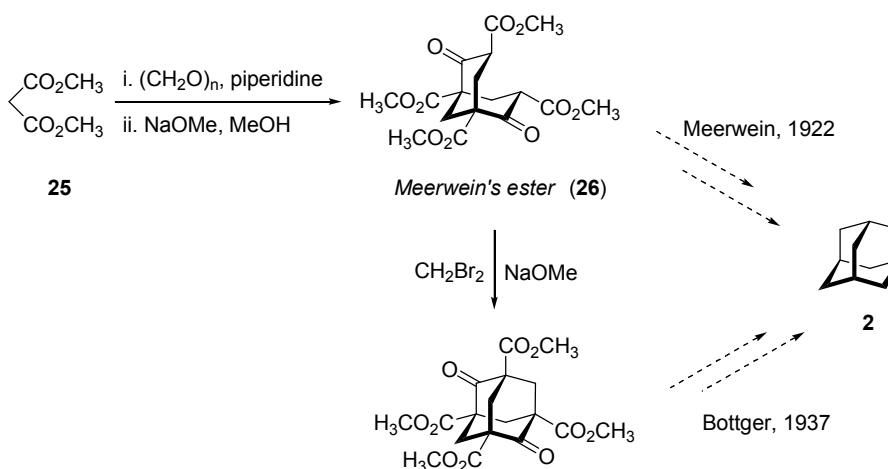


1.2. Syntheses of Diamondoid Hydrocarbons: History and Perspectives

1.2.1. Early Synthetic Efforts to Adamantane

The earliest attempt to make adamantane (**2**) or its derivatives dates back to 1922, eleven years before adamantane was even isolated from petroleum. The ester **26**, named after Meerwein, was prepared by condensing formaldehyde with dimethyl malonate (**25**) (Scheme 5).¹³ Unfortunately, Meerwein's attempt to add a methylene bridge to the ester **26** to produce the adamantane carbon framework was unsuccessful. Fifteen years later, Böttger managed to make the framework of adamantane (**2**) by treating the Meerwein's ester (**26**) with NaOMe and CH_2Br_2 .¹⁴ However, he failed to produce adamantane (**2**) from the various precursors he synthesised.

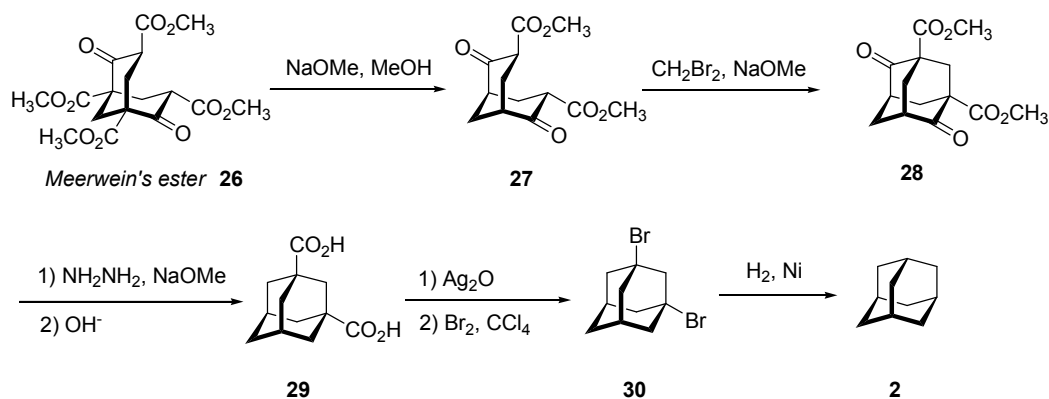
Scheme 5. The attempted syntheses of adamantane (**2**) by Meerwein and Böttger.



The tough synthetic problem was finally solved by Prelog and Seiwerth in 1941, which also allowed the first solid structural confirmation of the cage hydrocarbon adamantane (**2**) since its isolation eight years previously.³ Instead of starting from Meerwein's ester (**26**), Prelog used a less highly functionalised diester **27** by first removing two carbomethoxy groups from ester **26**, then inserted a methylene bridge to generate the adamantane skeleton **28** (Scheme 6). Wolff-Kishner reduction of di-keto compound **28** followed by saponification

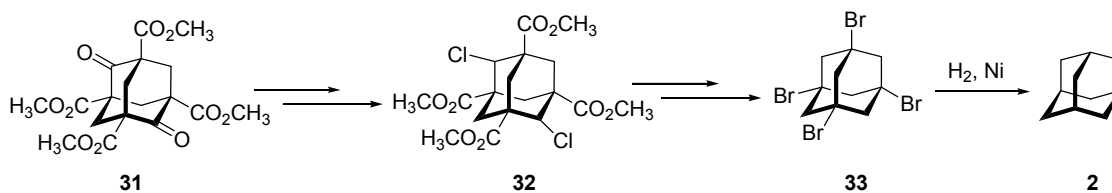
led to dicarboxylic acid **29**. Adamantane (**2**) was finally obtained in three routine steps from dicarboxylic acid **29**. Although the synthesis was of great importance to early synthetic chemistry, the extremely low yield (0.3% overall) overshadowed its success.

Scheme 6. The first synthesis of adamantane (**2**) by Prelog.



The synthesis of adamantane (**2**) was further improved by Stetter in 1956 with an increased overall yield of 6% (Scheme 7).¹⁵ Stetter synthesised dichloro compound **32** from the tetra-ester **31** which was originally utilised by Böttger. Dichloro compound **32** was then converted to tetra-bromide **33**, which was transformed to the desired adamantane (**2**) upon hydrogenation.

Scheme 7. Stetter's improved synthesis of adamantane (**2**).

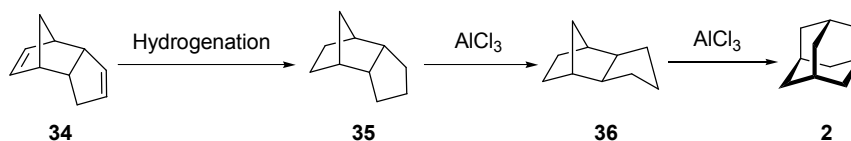


1.2.2. Schleyer's Remarkable Synthesis of Adamantane

Diamondoid hydrocarbon chemistry was revolutionised by Schleyer when he made the chance discovery of an elegant and remarkably simple method for the preparation of adamantane (**2**) in 1957.¹⁶ His discovery marked a new era for this chemistry and transformed this field into the flourishing and promising research area it is today.

Originally, Schleyer planned to carry out a Lewis-acid catalysed isomerisation of the less stable *endo*-tetrahydrodicyclopentadiene **35** (readily available from hydrogenation of dicyclopentadiene **34**) to the more stable *exo*-isomer **36** (Scheme 8). To his surprise, after distillation of lower boiling point compounds, there were still white crystals left in the flask which later proved to be adamantane (**2**). The secret of his lucky success was his appreciation of the fact that adamantane was the most stable hydrocarbon of formula C₁₀H₁₆. Even though the yield of this reaction was low (15-20%) due to the concomitant formation of numerous by-products, it had a great consequence for the diamondoid hydrocarbon chemistry. As McKervery commented, "Not only did this discovery make adamantane immediately available but it also established the pattern of much subsequent research in this area".¹⁷

Scheme 8. Schleyer's remarkable synthesis of adamantane (**2**).



Many efforts have been made over the years to improve the yield of Schleyer's isomerisation method to synthesise adamantane (**2**), with the main focus being on the choice of Lewis acid catalysts and operating conditions.¹⁸ One improvement made was from the use of sludge catalysts, which refer to mixed catalysts of aluminium halide and hydrogen halide. This kind of catalyst was believed to have a longer lifetime and improved the yield of the isomerisation process to 40%.¹⁹ A gas-phase process using a

solid-supported catalyst was also examined. McKervery further improved the yield to 60% by employing gaseous **35** in dry HCl passing through a hot tube containing a chlorinated palladium-alumina catalyst.²⁰ Dramatic improvement in yield (20 – 80%) was accomplished by Olah through using a variety of liquid and solid superacid catalysts to isomerise hydrocarbon **35** to adamantane (**2**).²¹ The highest yields were obtained with the superacids of $\text{CF}_3\text{SO}_3\text{H} + \text{SbF}_5$ (1:1) and $\text{CF}_3\text{SO}_3\text{H} + \text{B}(\text{OSO}_2\text{CF}_3)_3$ (1:1).

With regard to the rearrangement mechanism, a general mathematical model for analysing possible rearrangement pathways developed by Whitlock and Siefken, showed that there were 2897 possible routes between precursor **35** and adamantane (**2**).²² Although it is easy to rule out some energetically disfavoured pathways, to date no one has actually put forward a single mechanistic pathway to elucidate the rearrangement. Not surprisingly, the rearrangement mechanism includes hydride abstraction and subsequent 1,2-hydride shifts and Wagner-Meerwein rearrangements (1,2-carbon shift). Without any doubt, the driving force for the isomerisation of precursor **35** to adamantane (**2**) is the extremely high thermodynamic stability of strain-free adamantane. This results from the “high degree of branching in the ring system and the nearly ideal positioning of all atoms in the whole molecular structure”.²³ According to X-ray analysis and electron diffraction data, adamantane (**2**) has a set of ideal structural parameters with carbon-carbon bond angles of 109.5° and bond lengths of 1.54 Å.

The above theory indicates that every hydrocarbon with a molecular formula of $\text{C}_{10}\text{H}_{16}$ would rearrange to the thermodynamically most stable isomer adamantane (**2**) eventually. Indeed, the rearrangement precursor to adamantane (**2**) needs not necessarily to be tetrahydrodicyclopentadiene **35**. There are quite a few other known C_{10} tricycloalkane precursors, such as twistane (**37**), tricyclo[5.2.1.0]decane (**38**), protoadamantane (**39**) and 2,6-trimethylenenorbornane (**40**) that can serve as the rearrangement precursors to adamantane (**2**) (Figure 2).¹⁸

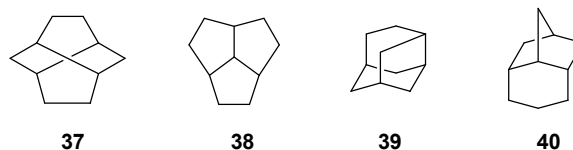
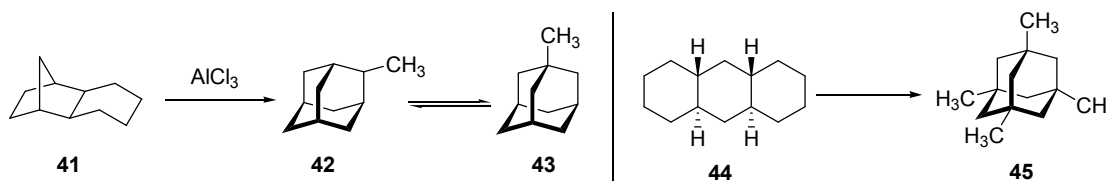


Figure 2. Structures of other rearrangement precursors to adamantane (2).

It is noteworthy to mention that even non-isomeric precursors can be isomerised to alkylated adamantane. For example, *cis,exo*-2,3-tetramethylenenorbornane (**41**) rearranges to a mixture of 2-methyl adamantane (**42**) and 1-methyl adamantane (**43**) (Scheme 9). Schneider from Sun Oil Company showed that even a strain-free *trans-syn-trans* isomer of perhydroanthracene (**44**) was isomerised to 1,3,5,7-tetramethyladamantane (**45**), with the only driving force resulting from the greater degree of chain branching in the cage product **45** (Scheme 8).²⁴

Scheme 9. Hydrocarbon precursors rearranged to adamantane derivatives.



1.2.3. Synthesis of Diamantane

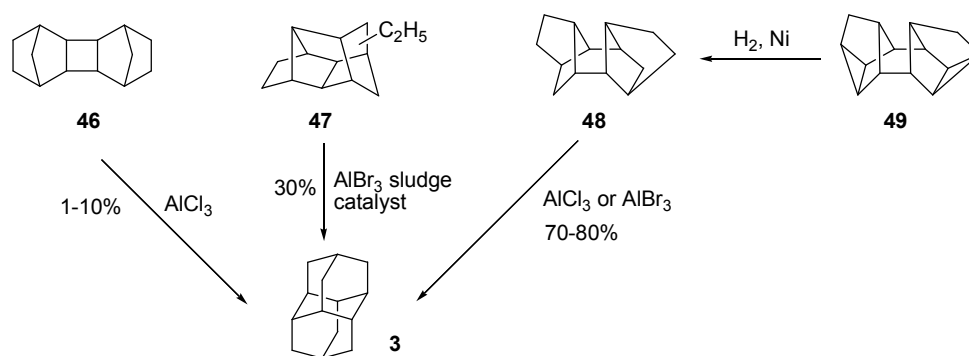
Diamantane (**3**) (Figure 1) is also known as “congressane” since it served as a logo for an IUPAC congress held in London in 1963, where chemists faced the challenge of making this hydrocarbon after the successful adamantane synthesis by Schleyer. The application of Schleyer’s significant isomerisation method to the syntheses of larger diamondoid hydrocarbons soon became the focus of much research: how far could this method be extended? What are the structural requirements for the rearrangement precursors?

In fact, the application of the rearrangement route to the synthesis of diamantane (**3**) highlighted the extension of Schleyer’s method to the more complex diamondoid

hydrocarbons. Of significant importance is the choice of a suitable hydrocarbon precursor which is crucial for the successful rearrangement. The precursor should be readily available, be isomeric with the desired diamondoid structure and should possess a moderate degree of strain to ensure, to some extent, a thermodynamic driving force.¹⁸ Another significant aspect of the rearrangement process is that it must be mechanistically reasonable. In other words, only energetically accessible carbocation intermediates can be involved and the necessary 1,2-hydride shift and Wagner-Meerwein rearrangements will only take place when the intermediate has favourable bond alignments.

The importance of the choice of a suitable precursor was highlighted effectively by the syntheses of diamantane (**3**) from the various precursors outlined in Scheme 10. Schleyer first obtained diamantane (**3**) from the norbornene [2 + 2] photodimer **46** in 1-10% yield depending on which isomer of **46** was used.²⁵ Later, the same research group demonstrated that diamantane (**3**) could be obtained in 30% yield from pentacyclic precursor **47**, which was not readily available.²⁶ A much more effective isomerisation (70-80% yield) was realised by McKervy in Belfast starting from the isomeric precursor **48**, which was obtained from the hydrogenation of [4 + 4] dimerisation of norbornadiene (also known as binor-S (**49**)).²⁷

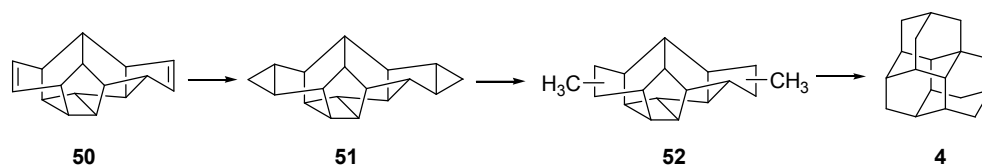
Scheme 10. Syntheses of diamantane (**3**) from various rearrangement precursors.



1.2.4. Synthesis of Triamantane

Once again, the development of the triamantane (**4**) synthesis illustrates the importance of the choice of suitable rearrangement precursors. As for diamantane (**3**), the synthesis of triamantane (**4**) initially started from inefficient precursors and was followed by the search for more suitable precursors. The cyclooctatetraene dimer **50** was used as a source of a C₁₆ isomer, which was converted to a C₁₈ isomer **51** by a double Simmons-Smith cyclopropanation of both carbon-carbon double bonds (Scheme 11). The hydrogen content was then further corrected by hydrogenolysis to furnish the rearrangement precursor **52**.²⁸ However, the low yield (1%) of the isomerisation process failed to satisfy the chemical community, and this prompted other research groups to search for better hydrocarbon rearrangement precursors.

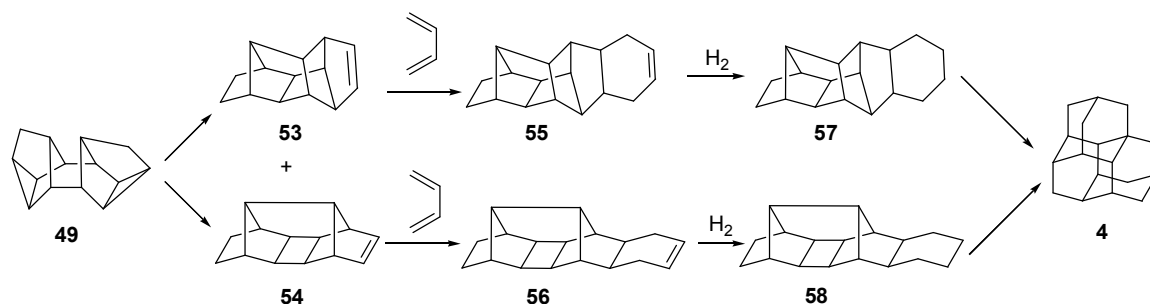
Scheme 11. Synthesis of triamantane **4** from precursor **33**.



A big improvement towards the synthesis of triamantane (**4**) was effected by McKervery and co-workers.^{29,30} Encouraged by the remarkably simple synthesis of diamantane (**3**) from heptacyclic binor-S (**49**) with the molecular formula of C₁₄H₁₆ (Scheme 10), they planned to construct triamantane (**4**) from derivatives of binor-S (**49**). The difference between target triamantane (**4**) and binor-S (**49**) is C₄H₈ and both of the molecules are heptacyclic. So the question was how to add four carbons onto binor-S (**49**) or its isomer without adding an extra ring. McKervery and co-workers cleverly solved this problem by first rearranging highly strained binor-S (**49**) to a mixture of hexacycles **53** and **54**, by carrying out one cyclopropane ring opening and a subsequent transannular process (Scheme 12). This process occurred in both solution and gas phase conditions. The carbon content was then corrected by adding cyclobutadiene to hexacycles **53** and **54** by a Diels-Alder reaction. The subsequent hydrogenation of the resulting cycloadducts **55** and

56 afforded products **57** and **58**, respectively, with the desired molecular formula of $C_{18}H_{24}$. Isomerisation of the $C_{18}H_{24}$ isomers **57** and **58** catalysed by $AlCl_3$ in hot cyclohexane produced triamantane (**4**) in 60% yield. This yield was later improved to 80% by Olah and co-workers by employing $B(OSO_2CF_3)_3$ in Freon-113 as a catalyst.³¹

Scheme 12. Syntheses of triamantane (**4**) from binor-S (**49**) derivatives.



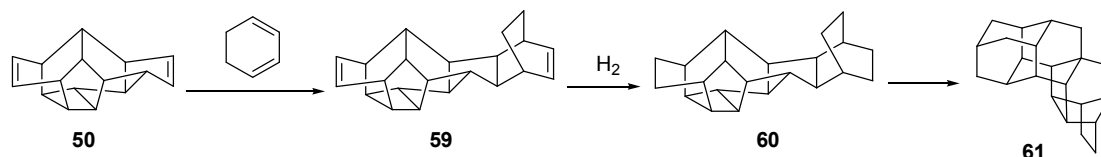
1.2.5. Synthetic Efforts to the Higher Diamondoid Tetramantane

Adamantane (**2**), diamantane (**3**) and triamantane (**4**) are viewed as lower diamondoid hydrocarbons, each of which exists in a single isomeric form. They are now readily available from cationic rearrangements as discussed above. The higher diamondoid hydrocarbons, which possess structural isomers start with tetramantanes, and their syntheses become increasingly more difficult due to their increasing sizes.

The challenge was first taken by Schleyer, who took the advantage of the cyclooctatetraene dimer **50** that he used in the synthesis of triamantane (**4**). Hydrogenation of the cycloadduct **59** derived from the Diels-Alder reaction between dimer **50** and cyclohexadiene gave strained polycycle **60** ($C_{22}H_{28}$), which is isomeric to tetramantane (Scheme 13).³² Unfortunately, under no conditions did precursor **60** rearrange to any of the desired tetramantanes. In contrast, the rearrangement stopped at compound **61** bearing only two completed adamantane units. Since tetramantanes are thermodynamically more stable than hydrocarbon **61** which has a highly strained norbornane unit, it must be a kinetic factor that

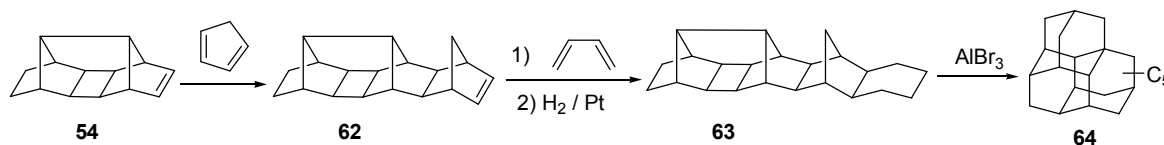
accounts for this failure. Increasing reaction times and temperatures only led to decomposition. It is clear that at this stage, “the crucial cationic intermediate necessary for initiating the next step, or a bond shift associated with that step, is inaccessible high in energy”.¹⁷

Scheme 13. Attempt to synthesise tetramantanes by Schleyer.



McKervey and co-workers took advantage of hexacycle **54** derived from isomerisation of binor-S (**49**) to add three rings and eight carbons by sequential Diels-Alder cycloaddition with cyclopentadiene and butadiene followed by hydrogenation. In this way, they synthesised polycyclic compound **63** with one extra carbon compared to the carbon content of the desired tetramantane (Scheme 14).¹⁸ It is well believed that precursors containing extra carbons will always rearrange to alkyl-substituted polymantanes rather than the less regular structures without alkyl substituents.¹⁸ Isomerisation of polycyclic hydrocarbon **63** with catalytic Lewis acid was expected to produce methyltetramantanes. However, the rearrangement gave an inseparable mixture of hydrocarbons, among which no desired products were detected. By gas-phase catalysed degradation of these mixtures at high temperature, the hydrocarbon products were thought to be structures of type **64** consisting of a complete triamantane unit to which is attached an irregular C₅ unit.¹⁸

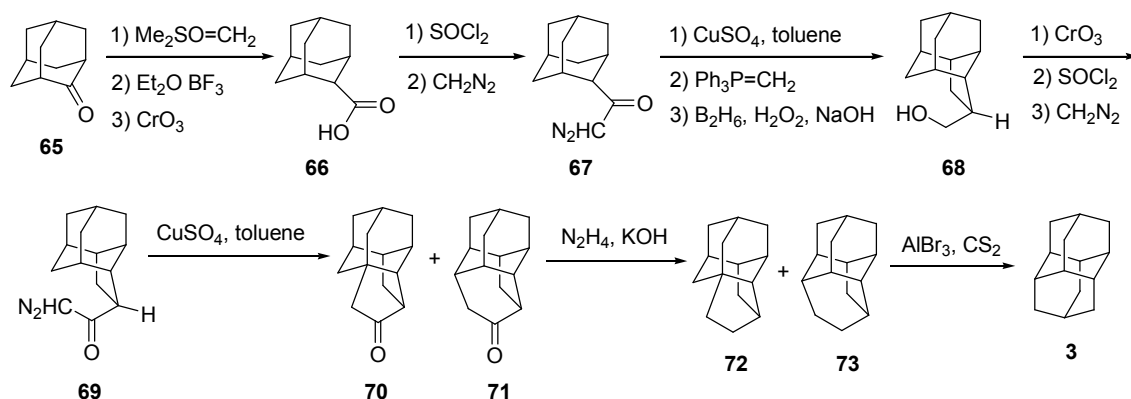
Scheme 14. Attempt to synthesize tetramantane by McKervey.



1.2.6. Stepwise Homologation Approach to Diamondoid Hydrocarbons

The failure to produce tetramantanes through aluminium halide catalysed rearrangement inspired chemists to pursue alternative approaches. This time, the success was based on the stepwise syntheses of diamantane (**3**) independently developed by Schleyer³³ and McKervey³⁴ and its extension to higher diamondoid hydrocarbons. Schleyer's stepwise synthesis of diamantane (**3**) is detailed in Scheme 15. Carboxylic acid **66** was obtained from ketone **65** in three steps, which was further converted to α -diazoketone **67**. Then diazoketone **67** underwent carbene insertion to one of the adamantane methylene groups to generate a new five-membered ring. A Wittig reaction followed by hydroboration furnished alcohol **68**. Again, routine reactions of alcohol **68** provided a new α -diazoketone **69**, which then gave a mixture of carbene insertion products **70** and **71** in the presence of copper catalyst to finish the task of adding four more carbons and two rings to adamantane (**2**). Wolff-Kishner reduction of ketones **70** and **71** removed the carbonyl groups to furnish hydrocarbons **72** and **73** isomeric to diamantane (**3**). Not surprisingly, catalysed rearrangement of hydrocarbons **72** and **73** afforded a quantitative conversion to diamantane (**3**).

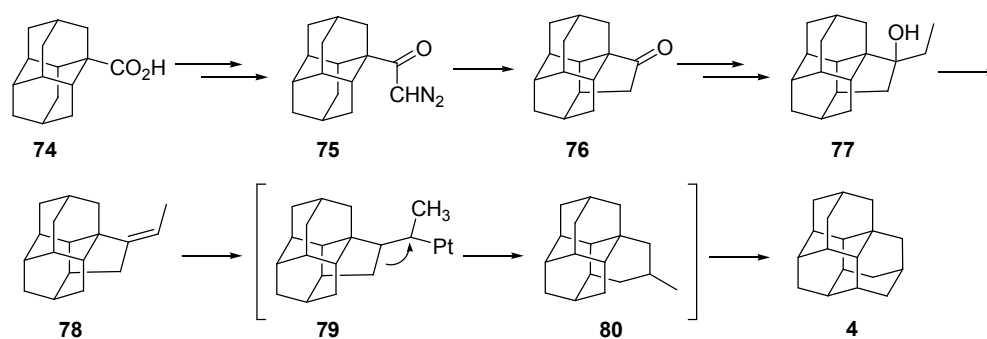
Scheme 15. Schleyer's stepwise synthesis of diamantane (**3**).



Thus, the single homologation of adamantane (**2**) to synthesise diamantane (**3**) had proved to be successful. The next goal was a single homologation of diamantane (**3**) to synthesise triamantane (**4**) and a double homologation of diamantane (**3**) to build tetramantane (**6**).

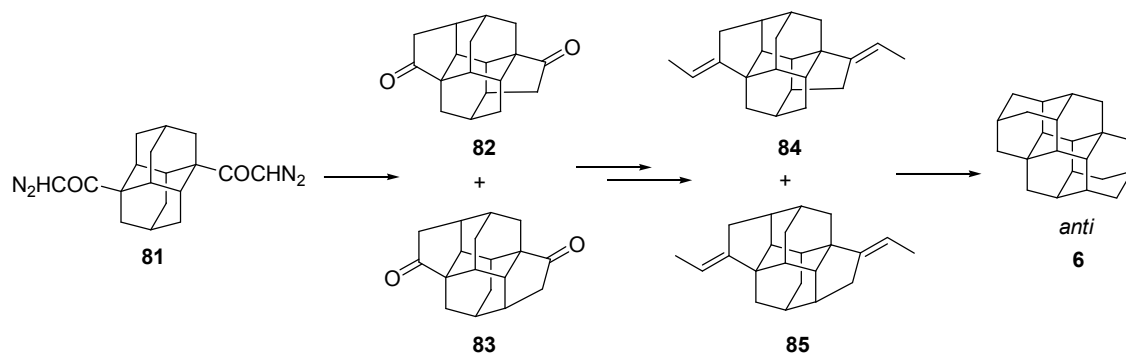
This time success came quickly. As detailed in the stepwise synthesis of diamantane (**3**), α -diazoketone **75**, obtained from diamantane-1-carboxylic acid (**74**) in two steps, underwent copper-catalysed carbene insertion to yield cyclopentanone **76** (Scheme 16).³⁴ Then ketone **76** was subjected to ethyl Grignard reagent addition, followed by dehydration to afford olefin **78**. The final rearrangement step was carried out with hydrogen in the gas phase over a platinum catalyst at 430 °C to produce triamantane (**4**) in 21% yield. Similar transformations are well known in the petroleum industry for catalytic reforming.³⁵ Although the mechanism remains controversial, the overall rearrangement process involves ring enlargement (**79** $\rightarrow$ **80**) *via* a 1,2-bond shift and dehydrocyclisation (**80** $\rightarrow$ **4**).

Scheme 16. McKervy's stepwise synthesis of triamantane (**4**).



The analogous double homologation of diamantane (**3**) to synthesise tetramantane (**6**) was carried out by the same research group (Scheme 17).^{36,37} Diamantane derivative **81** synthesised from diamantane-1,6-diol was converted to biscyclopentanones **82** and **83**. Then four more carbons were added through Grignard reaction and the resulting products were dehydrated to give the hydrocarbon rearrangement precursors **84** and **85**. Finally *anti*-tetramantane (**6**) was isolated in 10% yield by platinum catalysis in the gas-phase at 360 °C.

Scheme 17. McKervery's stepwise synthesis of *anti*-tetramantane (**6**).



1.2.7. Perspectives of Syntheses of Higher Diamondoid Hydrocarbons

Diamondoid hydrocarbon chemistry has been advancing rapidly over the past eighty years since its emergence in 1922 with Meerwein's first attempt to synthesise adamantane (**2**). Today, adamantane (**2**), diamantane (**3**) and triamantane (**4**) are readily accessible either by a catalysed rearrangement or a homologation approach. One of the three possible tetramantane isomers, *anti*-tetramantane (**6**), is the largest ever diamondoid hydrocarbon prepared by organic synthesis (by the homologation approach). This is the current stage of the syntheses of diamondoid hydrocarbons, which is an attractive research field with many synthetic challenges remaining.

Although the homologation approach to the syntheses of diamantane (**3**), triamantane (**4**) and *anti*-tetramantane (**6**) was successful, the main limitation of this methodology is that it is a multi-step procedure and the material (for example, *anti*-tetramantane (**6**)) produced by this approach has been of insufficient amount to enable chemists to explore further chemistry. From this point of view, Lewis-acid or superacid catalysed rearrangement is superior to the homologation approach, providing that a readily available and suitable precursor can be identified. The synthesis then becomes a remarkably easy "one step" operation. It remains unclear whether "the carbocation rearrangement route employing Lewis acid catalysts is limited to the lower polymantanes"¹² or not. There is still a lot of

synthetic work that needs to be done before making a final conclusion. It has been shown that although the liquid-phase methodology is limited, the catalytic gas-phase reaction may be promising for the syntheses of higher diamondoid hydrocarbons.¹⁸

1.3. Research Goals and Proposed Synthetic Work

1.3.1. Isolation of Cyclohexamantane and Research Goals

The isolation and structural determination of cyclohexamantane (**1**) from a distilled Gulf Coast petroleum was reported in 2003 by scientists from several research institutes.⁵ In fact, even before cyclohexamantane (**1**) was actually isolated, its structure had been used to represent a small diamond in theoretical studies.^{38,39} The structure ($C_{26}H_{30}$) was determined by single-crystal X-ray analysis, NMR, laser Raman spectroscopy and mass spectrometry, after crystals of cyclohexamantane (**1**) were obtained from crude petroleum by high-performance liquid chromatography (HPLC). The highly symmetrical hydrocarbon is a nanometer-sized diamond of approximately 10^{-21} carats with the point group of D_{3d} . The mean C-C distance is 1.538 Å, and the central C-C bond is significantly longer (1.568 Å). The mean C-C-C angle is 109.7°. A mass spectrum of cyclohexamantane (**1**) shows a large molecular ion (m/z 342) that is typical for unsubstituted diamondoid hydrocarbons. Cyclohexamantane (**1**) has a surprisingly high melting point (>314 °C in a sealed capillary tube).⁵

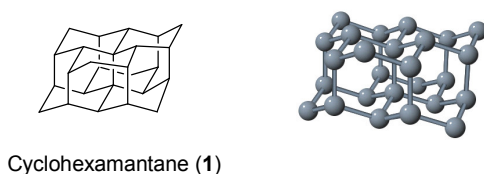


Figure 3. The structure of cyclohexamantane (**1**) and its carbon-framework.

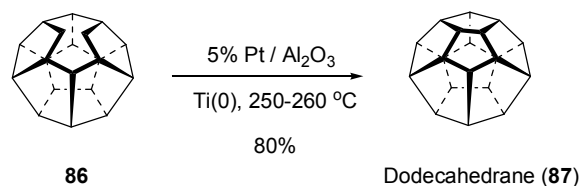
The extremely low concentration (less than 1 ppb) of cyclohexamantane (**1**) in its only natural source, petroleum, makes it very desirable to establish a concise synthetic strategy for its preparation and for further exploration of nano-diamondoid chemistry. It is clear that the natural synthetic route to cyclohexamantane (**1**) from hydrocarbon precursors must include an astronomical number of pathways and intermediates.⁵

Adapting the early achievements in Schleyer's synthesis of adamantane (**2**), as well as in the successful syntheses of diamantane (**3**) and triamantane (**4**) *via* thermodynamically controlled rearrangement of proper hydrocarbon isomers, our research goals are to prepare the rearrangement hydrocarbon precursors $C_{26}H_{32}$ and to study their dehydrogenative rearrangements to the target hydrocarbon cyclohexamantane ($C_{26}H_{30}$) (**1**).

Clearly our approach differs from the previous isomerisation methods in the literature, as our proposed rearrangement precursor has two extra hydrogen atoms compared to the target hydrocarbon cyclohexamantane (**1**). Although it is possible to prepare an isomeric precursor $C_{26}H_{30}$, this unique project aims to provide a novel approach to the rearrangement precursor $C_{26}H_{32}$ by either a four-directional synthesis or a Diels-Alder dimerisation approach starting from the readily available adamantane derivatives. Our proposed synthesis of the rearrangement precursor $C_{26}H_{32}$ by these two routes will be outlined in the sections **1.3.2** and **1.3.3**, and the results will be discussed in detail in the **Results and Discussion** section.

We anticipate that the dehydrogenative rearrangement of precursor $C_{26}H_{32}$ would furnish the target hydrocarbon cyclohexamantane (**1**) after losing one molecule of H_2 . Of course, this step would require considerable amounts of work to find out the optimal reaction conditions. Although, to our knowledge, this dehydrogenative rearrangement reaction is not well preceded in the literature, a similar transformation is well known in the petroleum industry for catalytic reforming.³⁵ Paquette also applied the dehydrogenative method for his synthesis of dodecahedrane (**87**).^{40,41} The remarkable transformation important to the Paquette approach is a dehydro-cyclisation to introduce the final pivotal carbon-carbon bond from the advanced intermediate **86**. This step involves utilisation of a mixture of finely divided titanium metal and 5% platinum on alumina as the dehydrogenation agent, and furnishes dodecahedrane (**87**) in excellent yield (Scheme 18).

Scheme 18. Dehydrogenative cyclisation of **86** to dodecahedrane (**87**) by Paquette.

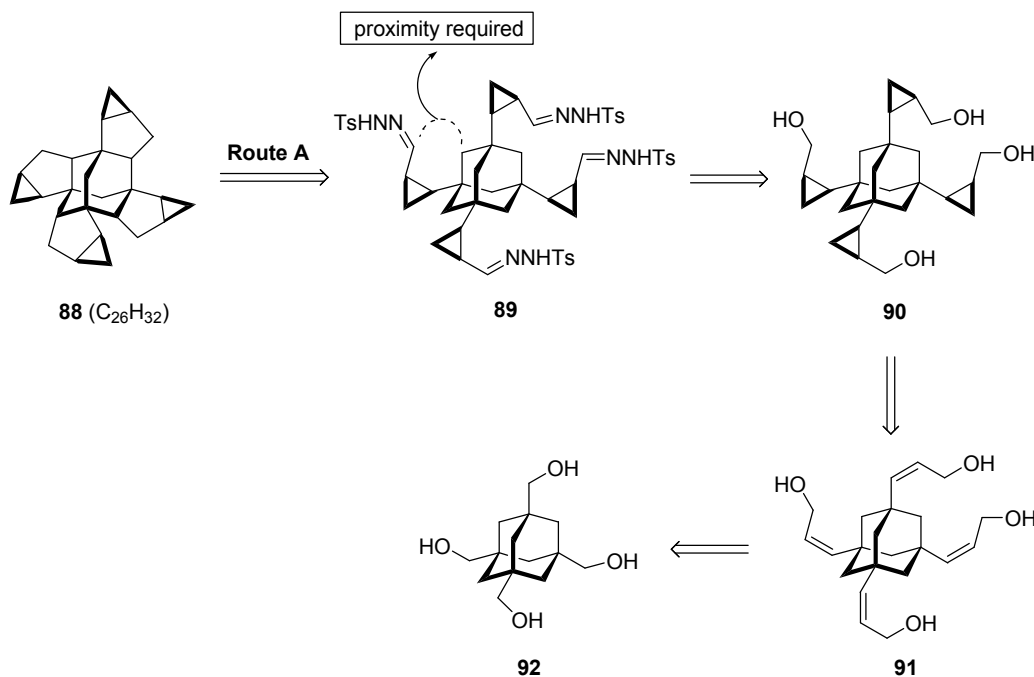


1.3.2. Four-Directional Synthesis Approach to Precursor C₂₆H₃₂

Our first proposed synthetic routes (**Route A** and **Route B**) to build the rearrangement hydrocarbon precursor **88** (C₂₆H₃₂) *via* a four-directional synthesis approach are outlined in Scheme 19 and Scheme 20.

In **Route A** (Scheme 19), the literature known adamantane derivative 1,3,5,7-tetrakis(hydroxymethyl)adamantane (**92**)⁴² will be converted to the tetra-(*Z*)-allylic alcohol **91**, followed by a Simmons-Smith cyclopropanation to provide the tetra-*syn*-cyclopropane **90** as a key intermediate in the synthesis. Oxidation of the tetra-ol **90** to the corresponding tetra-aldehyde and subsequent condensation with 4-toluenesulfonylhydrazine should produce the tetra-tosylhydrazone **89**. It was expected that the *syn*-cyclopropyl carbene intermediate generated from the salt of tetra-tosylhydrazone **89** should give the C-H insertion products. There are, of course, many possible insertions that can be observed, but these should provide hydrocarbon isomers which are expected to rearrange to the target molecule cyclohexamantane (**1**). For simplicity sake, the product is abbreviated as the tetra-cyclised compound **88** (C₂₆H₃₂), but it should contain other hydrocarbon isomers. It is noteworthy to mention that the cyclopropane units in compound **89** must have the *syn*-stereochemistry, in order to allow a close enough proximity of the adamantane methylene carbon and the carbene generated carbon in the insertion step (**89** → **88**) (Scheme 19). To this end, the four carbon-carbon double bonds in the cyclopropanation substrate **91** should all have the *cis* geometries.

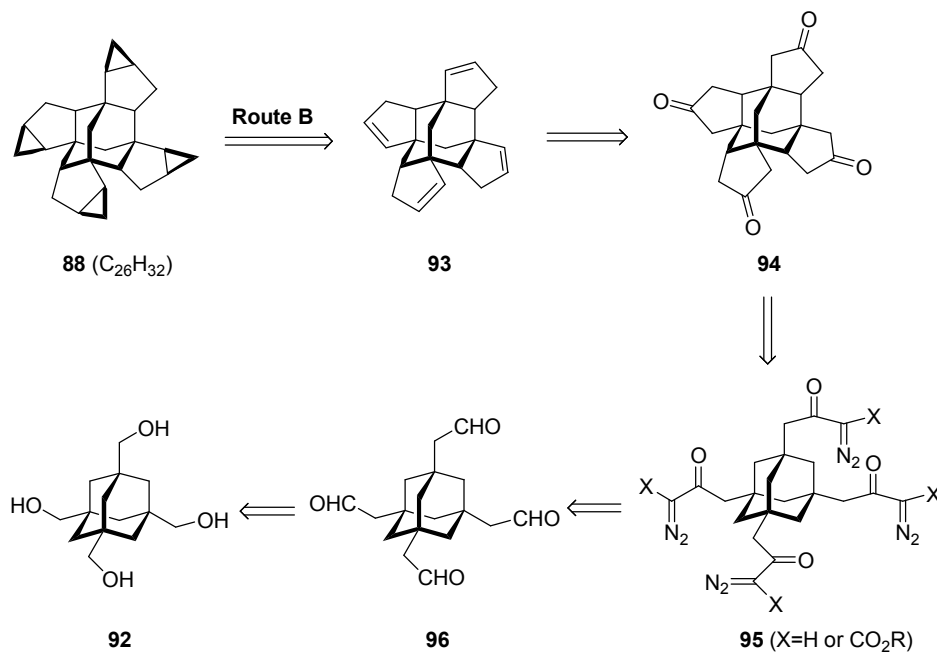
Scheme 19. Four-directional synthesis approach (**Route A**) to rearrangement precursor **88**.



Finally, exposure of the strained hydrocarbon **88** to either a Lewis acid or superacid using the gas-phase methodology is expected to provide the nano-diamond cyclohexamantane (**1**) after losing a molecule of hydrogen.

In contrast to **Route A**, **Route B** features an early stage carbene insertion and a late stage cyclopropanation (Scheme 20). Towards this goal, the tetra-diazo compound **95** will be constructed from tetra-aldehyde **96** which would be available from the known adamantane derivative tetra-ol **92**. Synthesis of the key intermediate adamantane tetra-cyclopentanone **94** will be achieved by the Rh(II) catalysed tetra-carbene insertion of tetra-diazo compound **95**, followed by removal of the X group (when X group is CO_2R). Reduction of tetra-cyclopentanone **94** to the corresponding alcohol followed by dehydration, or an equivalent process should lead to the tetra-olefin **93**. Once again, for simplicity sake, the compounds **94** and **93** only represent one of the many other possible regio- and stereo-isomers. It is then expected that tetra-cyclopropanation of tetra-olefin **93** would furnish the hydrocarbon rearrangement precursor **88** ($C_{26}H_{32}$).

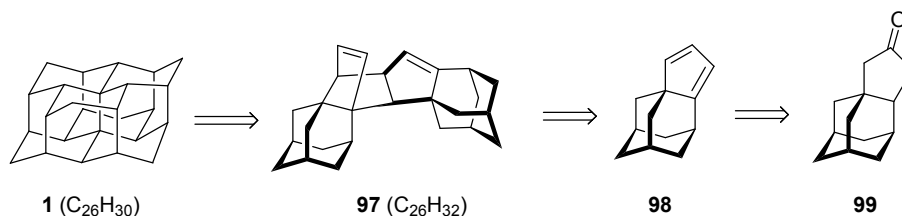
Scheme 20. Four-directional synthesis approach (**Route B**) to rearrangement precursor **88**.



1.3.3. Diels-Alder Dimerisation Approach to Precursor $C_{26}H_{32}$

A Diels-Alder dimerisation of the monomer adamantanocyclopentadiene **98** will be also studied as a more concise synthetic route to the hydrocarbon rearrangement precursor **97** ($C_{26}H_{32}$) (Scheme 21). The diene **98** would be derived from the literature known compound adamantanocyclopentanone **99**⁴³. Then Diels-Alder dimerisation of monomer **98** should lead to the dimer **97**, which serves as the dehydrogenative rearrangement precursor to the target molecule cyclohexamantane (**1**).

Scheme 21. Diels-Alder dimerisation approach to rearrangement precursor **97**.

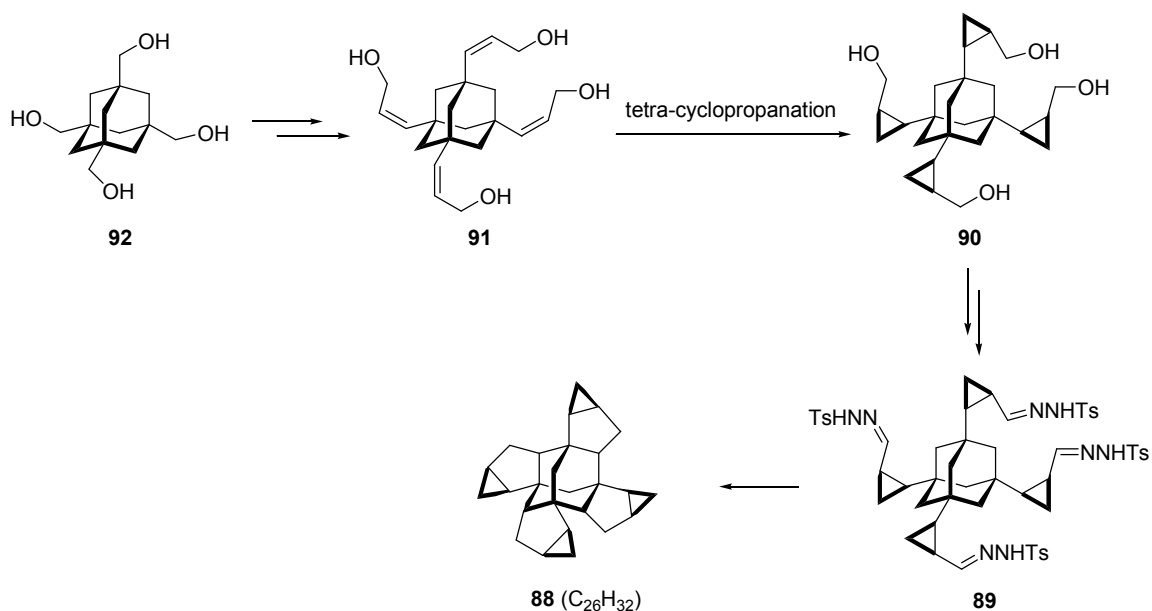


2. RESULTS AND DISCUSSION

2.1. Four-Directional Approach (Route A) to Rearrangement Precursor 88

As described in the previous chapter, two four-directional synthesis approaches (**Route A** and **Route B**) to build the hydrocarbon rearrangement precursor **88** were proposed. **Route A** features an early-stage cyclopropanation (**91** $\rightarrow$ **90**) and a late-stage carbene insertion (**89** $\rightarrow$ **88**) (Scheme 22). As mentioned previously in the **Introduction** section, it is important that the four olefins in the cyclopropanation substrate **91** should all possess *cis* geometry.

Scheme 22. Proposed four-directional synthesis approach (**Route A**) to precursor **88**.

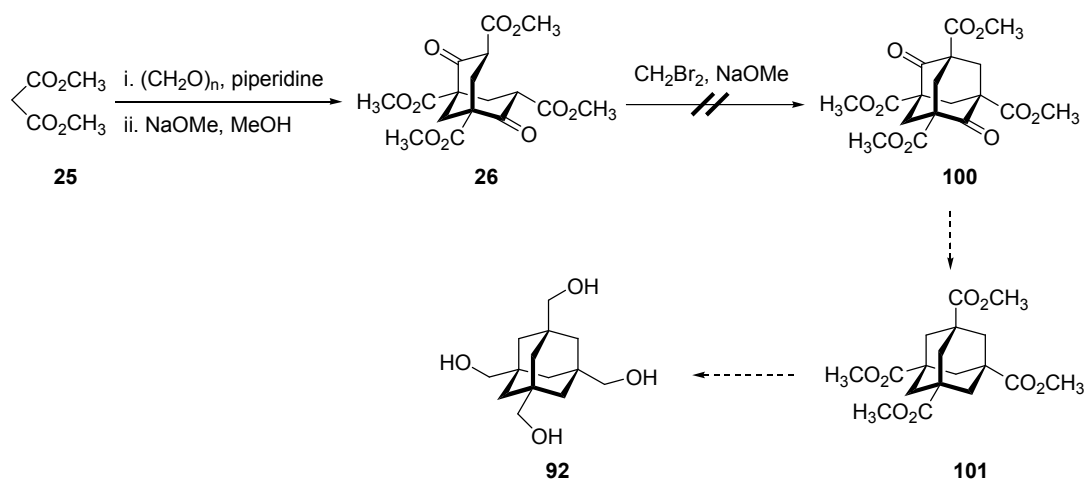


2.1.1. Synthesis of Tetra-(*Z*)-allylic Alcohol **91**

2.1.1.1. Attempted Synthesis of Adamantanetetramethanol (**92**) *via* Meerwein's Ester **26**

Route A commenced with the synthesis of adamantanetetramethanol (**92**), which was first described by Landa in 1959.⁴² The synthesis requires assembly of the polycyclic-substituted cage compound **100** from Meerwein's bicyclic ester **26** (Scheme 23). The preparation of Meerwein's ester **26** was achieved by reacting dimethyl malonate (**25**) with formaldehyde under basic conditions.⁴⁴ Although we tried to recrystallise the product from benzene several times, the purity of product **26** was still disappointingly low. We were able to obtain the pure product by flash chromatography, but the yield was less than 5%. The next step of adding a methylene bridge to Meerwein's ester **26** following the literature procedure in the same paper⁴² failed to furnish the desired tricyclic compound in our hands.

Scheme 23. Attempted synthesis of adamantanetetramethanol (**92**) *via* Meerwein's ester **26**.

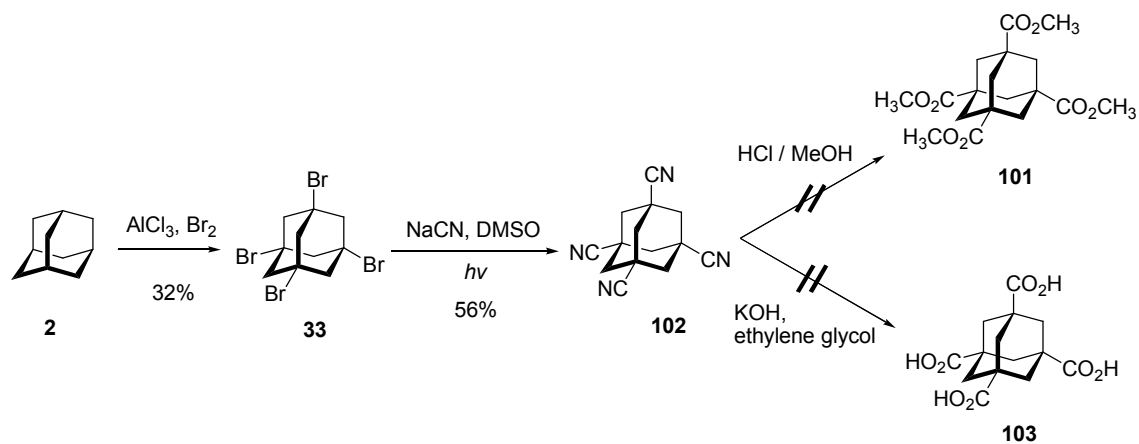


A quick review of this synthetic route to adamantanetetramethanol (**92**) *via* Meerwein's ester **26** reveals that the main drawbacks of this approach are low yielding steps of all the reactions involved and the high number of steps to the desired polycyclic tetra-ol **92**. In addition, a high-pressure and high-temperature bomb reaction was necessary in order to remove the carbonyl groups in compound **100** to synthesise tetra-ester **101**. These considerations led us to search for an alternative synthetic route to tetra-ol **92**.

2.1.1.2. Attempted Synthesis of Adamantanetetramethanol (**92**) via Tetra-cyanide **102**

Inspired by a recent paper⁴⁵, we carried out the synthesis of tetra-ol **92** via intermediate 1,3,5,7-tetracyanoadamantane (**102**) which was accessed from the cheap commercially available starting material adamantane (**2**) (Scheme 24). Using four equivalents of AlCl_3 following the exact literature procedure resulted in difficulty with stirring the reaction mixture and gave no desired product tetra-bromide **33**. To our delight, bromination of adamantane (**2**) using just one equivalent of AlCl_3 produced tetra-bromide **33** in 32% yield after recrystallisation from acetic acid.^{46,47} Photolysis at 254 nm of a mixture of tetrabromide **33** and NaCN in DMSO produced tetra-cyanide **102** in 56% isolated yield.⁴⁷ Unfortunately, both solvolysis of tetra-cyanide **102** with methanolic anhydrous HCl to give tetra-methyl ester **101** and hydrolysis of tetra-cyanide **102** to give tetra-carboxylic acid **103** failed to furnish any of the desired products (Scheme 24).⁴⁵ The lack of reactivity of the tetra-cyano compound **102** towards hydrolysis prompted us to abandon this route to adamantanetetramethanol (**92**).

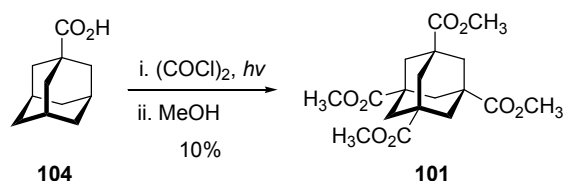
Scheme 24. Attempted synthesis of adamantanetetramethanol (**92**)
via 1,3,5,7-tetracyanoadamantane (**102**).



2.1.1.3. Photochemical Route to Adamantanetetramethanol (**92**)

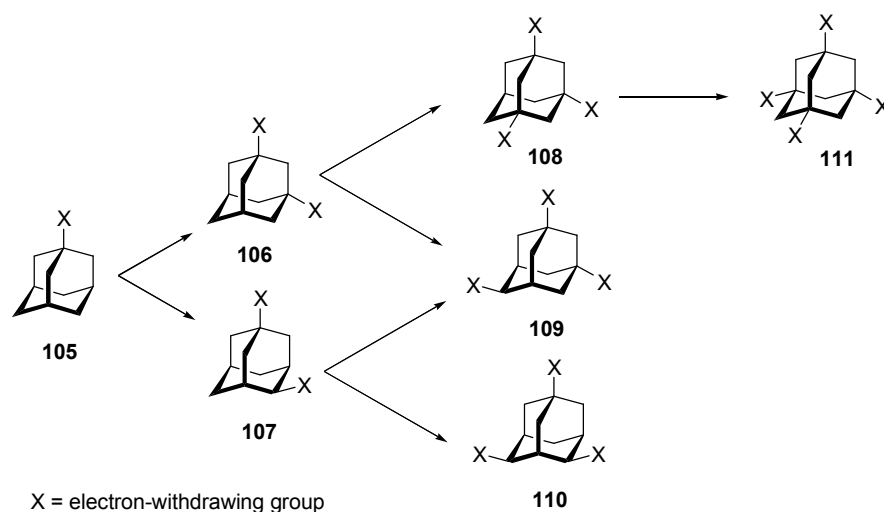
Extensive literature searches resulted in the discovery of an efficient transformation which carried out the photocarbonylation of 1-adamantanecarboxylic acid (**104**) in oxalyl chloride, followed by esterification with methanol to produce tetramethyl-ester **101** in one pot.⁴⁸ Following this procedure, the desired product 1,3,5,7-tetracarbomethoxyadamantane (**101**) was obtained in 10% yield from the commercially available 1-adamantanecarboxylic acid (**104**) (Scheme 25).

Scheme 25. Photochemical carbonylation of 1-adamantanecarboxylic acid (**104**).



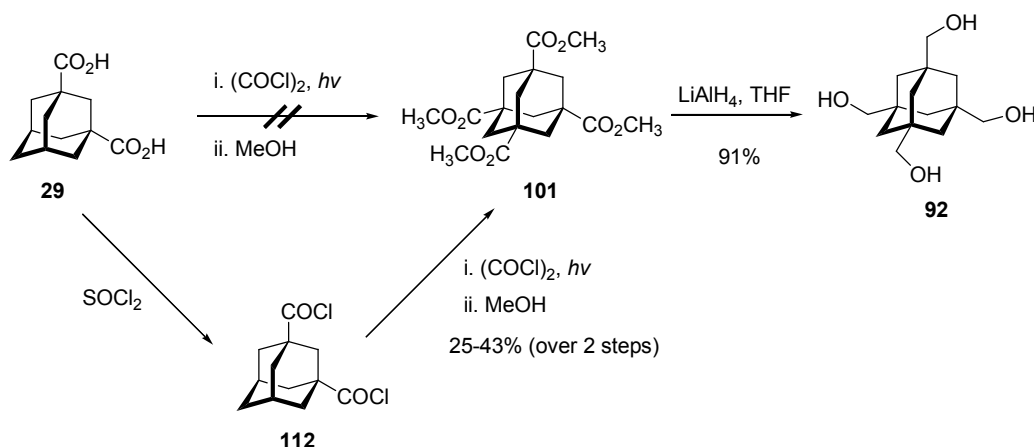
In this adamantane functionalisation, electron-withdrawing groups are used to direct substitutions predominantly to the remote positions (β or γ) rather than the *ortho* position.⁴⁹ It is also believed that in this process, hydrogens *ortho* to an electron-withdrawing group are less vulnerable to radical abstraction.^{50,51} According to the literature explanation for polysubstituted cubanes⁴⁹, we put forward a reaction pathway to better understand this photochemical process (Scheme 26). In fact, when we utilised GC-MS to follow the reaction progress, we indeed observed the generation of two di-substituted adamantanes (**106** and **107**) and three tri-substituted adamantanes (**108**, **109** and **110**) as shown in Scheme 26. It is obvious that only tri-substituted adamantane **108** can finally lead to the desired product **111**. Therefore, the low yield of the above reaction shown in Scheme 25 was due to the concomitant generation of lower (di- and tri-) substituted adamantanes as by-products.

Scheme 26. Reaction pathway of photochemical carbonylation of mono-substituted adamantane **105**.



Based on the above discussion, we proposed that the prepositioning of two carbonyl functional groups at adamantane bridgeheads should increase the yield of desired product **111**, since it can eliminate the two undesired pathways to by-products (**107** → **109** and **107** → **110** in Scheme 26). Towards this end, irradiation of a solution of commercially available 1,3-adamantanedicarboxylic acid (**29**) in oxalyl chloride in a Rayonet photochemical reactor following the exact literature procedure⁴⁸ was attempted. However, it didn't provide any of the desired product because of the low solubility of dicarboxylic acid **29** in oxalyl chloride (Scheme 27). To our delight, photochemical reaction of 1,3-adamantanedicarbonyl chloride (**112**)⁵², which was prepared from thionyl chloride and dicarboxylic acid **29**, gave the desired product 1,3,5,7-tetracarbomethoxyadamantane (**101**) in up to 43% yield over two steps. The product **101** could be easily isolated by simply triturating the crude product with the minimal amount of methanol. This significant increase in the reaction yield (from 10% to 43%) indeed proved our proposal. Then, lithium aluminum hydride reduction of tetra-ester **101** furnished adamantanetetramethanol (**92**) in 91% yield.

Scheme 27. Photochemical carbonylation route to adamantanetetramethanol (**92**).

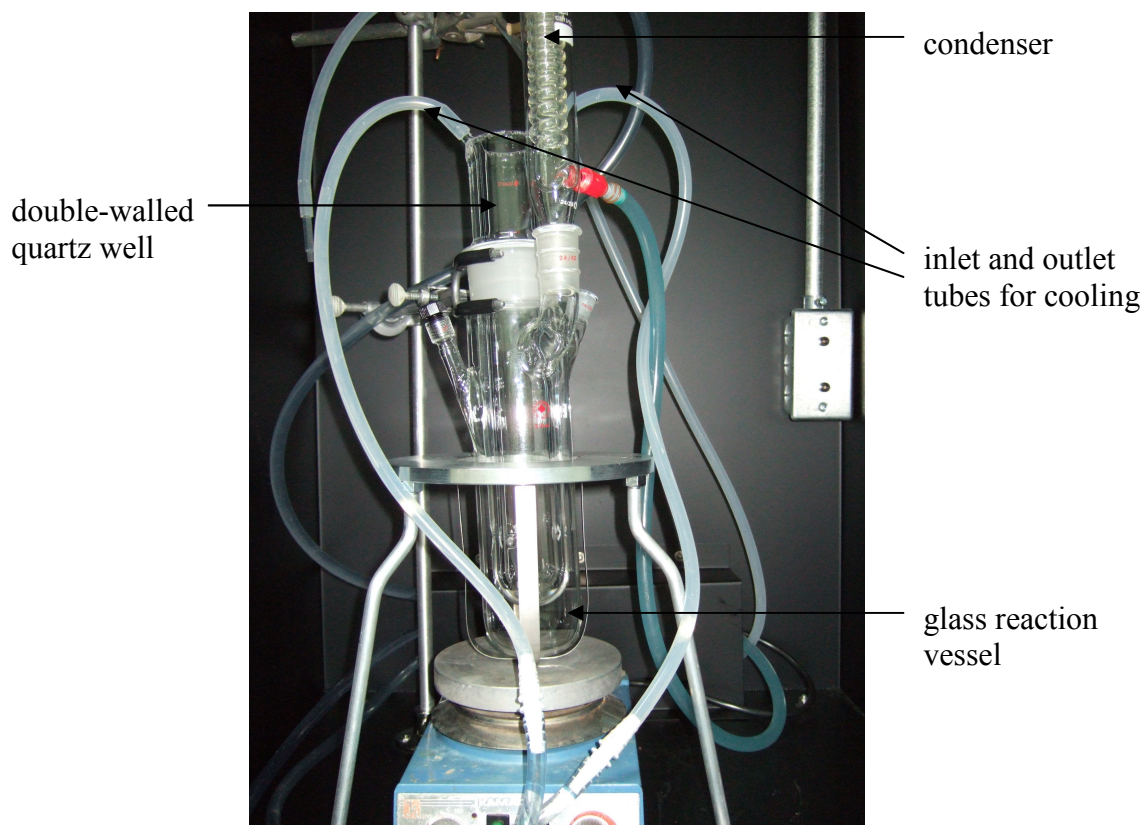


However, by using the Rayonet photochemical reactor in our group, the photocarbonylation of 1,3-adamantanediacyl chloride (**112**) to tetra-methyl ester **101** (Scheme 27) could only be carried out in a maximum of 2 grams scale, due to the size of the quartz reaction vessel available. This is also because the Rayonet photochemical reactor failed to provide enough energy for a large scale reaction, although eight low pressure mercury lamps (100 W each) were utilised to produce the UV irradiation at 254 nm.

Pleasingly, a large scale photocarbonylation reaction by using a different reaction assembly was carried out during an industrial placement in Molecular and Health Technologies in CSIRO (Commonwealth Scientific and Research Organisation), Australia. Picture 1 shows the photochemical reaction assembly. Medium pressure, quartz and mercury-vapour lamp (450 W) was immersed into the double-walled quartz well with inlet and outlet tubes for cooling. The glass reaction vessel having a vertical joint for condenser was placed outside the immersion well. Of total energy the lamp radiated, approximately 40-48% is in the UV region of the spectrum and 40-43% is in the visible, with the balance in the infrared. Although the UV output between 220 nm and 280 nm, which is the requisite wavelength for our photochemical dissociation, is only about 27 W, this reaction setup is more efficient than using the Rayonet reactor. This efficiency is largely due to the fact that the lamp is in the middle of the reaction vessel, thus most of the energy is absorbed by the reaction without significant loss. Now we are able to carry out the photochemical reaction of

12 grams of di-acid chloride **112** by using this setup. Although the yield of this large scale reaction has dropped to 25%, we are able to produce the desired product **101** in large quantities in a short time.

Picture 1. The large scale photochemical reaction assembly.

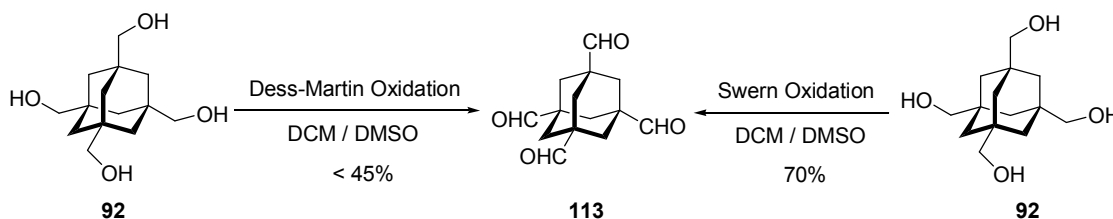


2.1.1.4. Synthesis of Tetra-(Z)-allylic Alcohol **91**

Tetra-ol **92** is a very polar compound and consequently only soluble in solvents such as MeOH, THF or DMSO. Thus, we first tried the Dess-Martin oxidation of tetra-ol **92** (50 mg scale) in a mixed-solvent system (DCM/DMSO, 2:1) that is necessary to dissolve the substrate, and the corresponding tetra-aldehyde **113** was obtained in 45% yield (Scheme 28). However, a larger scale oxidation using Dess-Martin periodinane resulted in a decrease in yield (32% yield for 80 mg scale). As an alternative, we next tried Swern

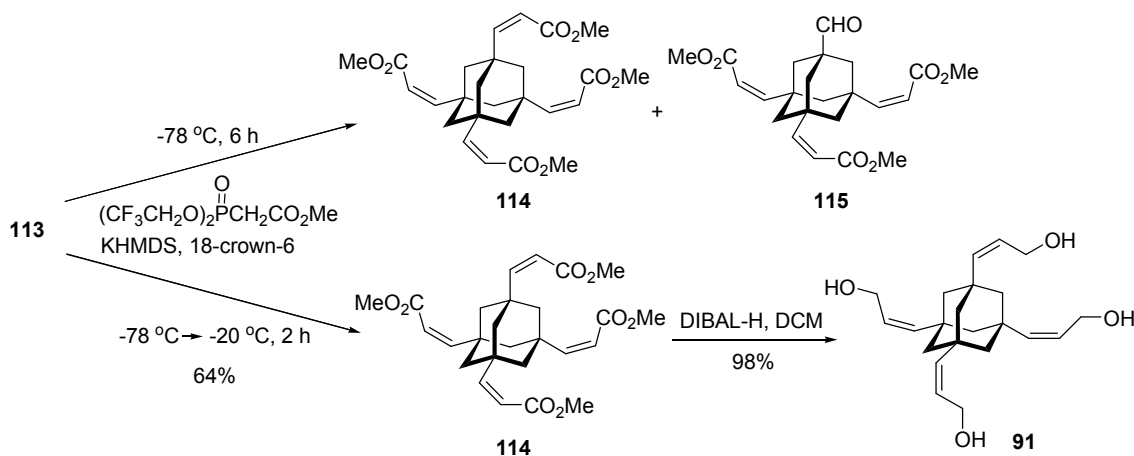
oxidation of tetra-ol **92** in the same mixed-solvent system (DCM/DMSO).⁵³ Fortunately, the Swern oxidation proved to be a reliable reaction and gave the product tetra-aldehyde **113** in a significantly better yield (70%) for the large scale reaction (1 g scale).

Scheme 28. Oxidation of tetra-ol **92** to tetra-aldehyde **113**.



With tetra-aldehyde **113** in hand, (*Z*)-selective Horner-Emmons reaction of **113** under Still-Gennari conditions⁵⁴ at $-78\text{ }^{\circ}\text{C}$ provided an inseparable mixture of the desired product **114** and the incomplete olefination product **115** (Scheme 29). Longer reaction times failed to drive the reaction to completion, however warming the reaction mixture to $-20\text{ }^{\circ}\text{C}$ for a period of 2 hours furnished tetra-olefin **114** as the sole product in 64% yield. From ^1H NMR spectroscopy, the coupling constant J between two olefinic protons is 13.1 Hz. This indicates all four carbon-carbon double bonds in tetra-ester **114** possess the desired *cis* geometry by comparing the J value with a similar system in the literature.⁵⁵

Scheme 29. Synthesis of tetra-(*Z*)-allylic alcohol **91** from tetra-aldehyde **113**.



We next carried out the DIBAL-H reduction of tetra-ester **114** to provide the tetra-(*Z*)-allylic alcohol **91** in excellent yield (Scheme 29). In order to unambiguously determine the geometry of the olefins, X-ray quality crystals of tetra-ol **91** were successfully grown from a 1:1 mixture of methanol and toluene at low temperature (4 °C). The graphic representation of the X-ray crystal structure of tetra-(*Z*)-allylic alcohol **91** is shown in Figure 4, from which it is clear that all four carbon-carbon double bonds in **91** possess the requisite *cis* geometry.

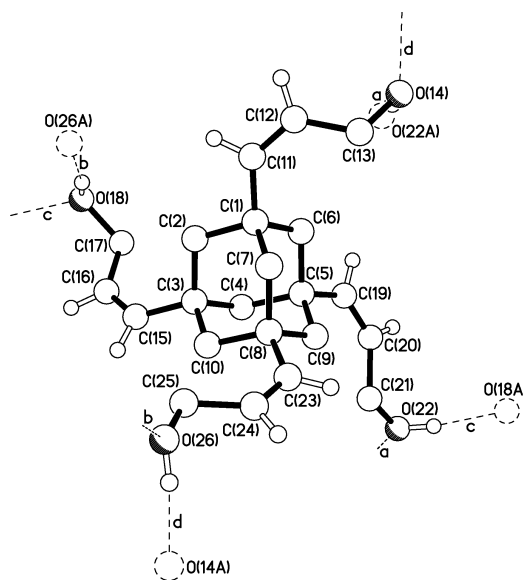


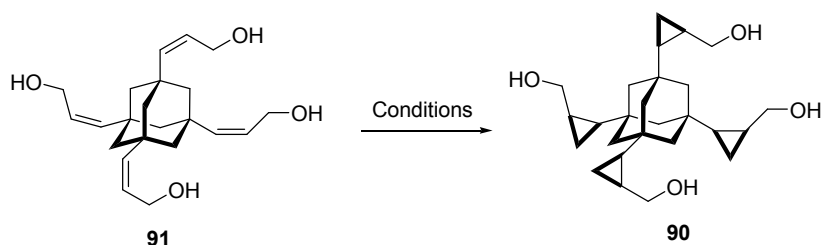
Figure 4. Graphic representation of X-ray crystal structure of tetra-(*Z*)-allylic alcohol **91**.

2.1.2. Synthesis of Key Intermediate Tetra-*syn*-cyclopropane **90**

2.1.2.1. Attempted Synthesis of **90** by Direct Cyclopropanation

Having successfully synthesised tetra-(*Z*)-allylic alcohol **91**, the key tetra-cyclopropanation reaction was next investigated. Due to the low solubility of the polar tetra-ol **91**, we first elected to carry out the samarium-promoted cyclopropanation in THF (Table 1). However, use of samarium/mercury amalgam in conjunction with either diiodomethane (Entry 1, Table 1) or chloriodomethane (Entry 2, Table 1) to generate samarium carbenoids, failed to furnish any desired product **90**.⁵⁶ Changing the samarium source to SmI₂ produced no desired product either (Entry 3, Table 1).⁵⁶ We then examined the powerful Simmons-Smith cyclopropanation using Charette's improved procedure.⁵⁷ Although the cyclopropanation substrate **91** has very low solubility in the required solvent CH₂Cl₂, it was anticipated that, the intermediate zinc-alkoxide species formed from Zn(CH₂I)₂ and tetra-ol **91** would desymmetrise the substrate to some extent, thus solving the solubility problem. Unfortunately, this reaction failed to give rise to any desired product with only starting material recovered (Entry 4, Table 1).

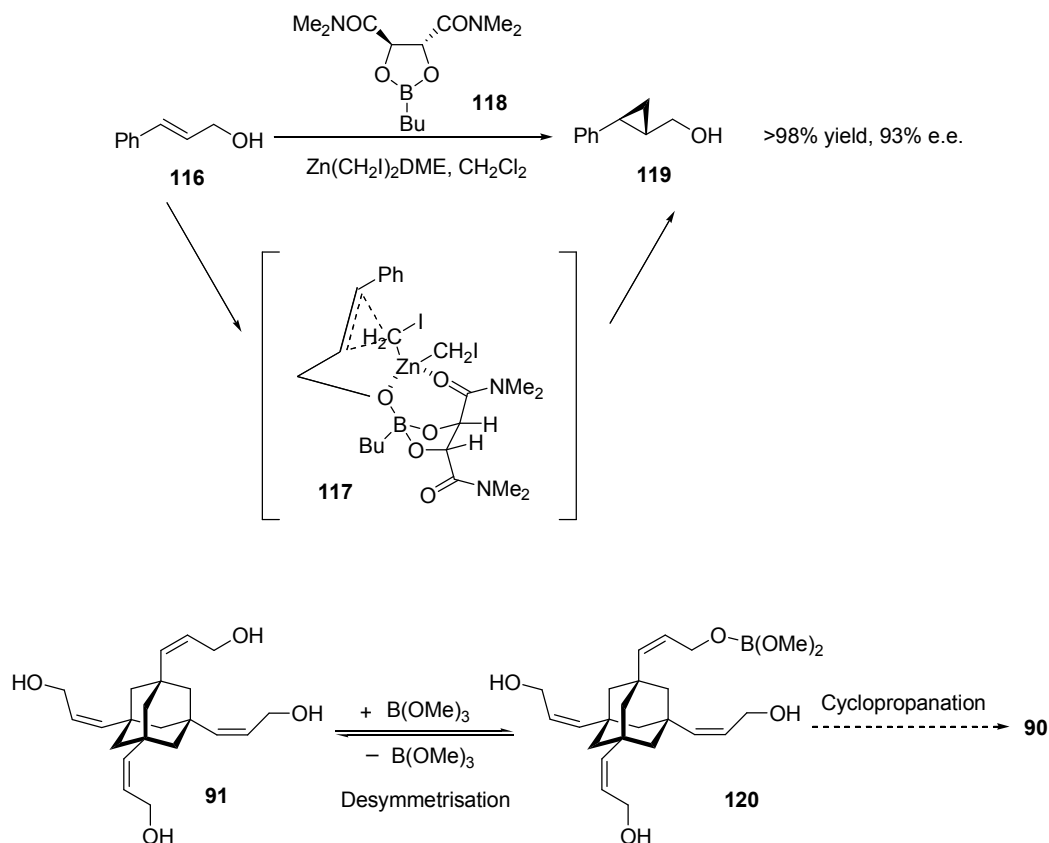
Table 1. Studies on direct cyclopropanation of tetra-ol **91**.



Entry	Reaction Conditions	Results
1	Sm(Hg), CH ₂ I ₂ , THF, -78 °C to r.t., 16 h	No desired product.
2	Sm(Hg), ICH ₂ Cl, THF, -78 °C to r.t., 18 h	No desired product.
3	SmI ₂ , ICH ₂ Cl, THF, -78 °C to r.t., 20 h	No desired product.
4	Zn(CH ₂ I) ₂ DME, CH ₂ Cl ₂ , -15 °C to r.t., 22 h	Starting material recovery.

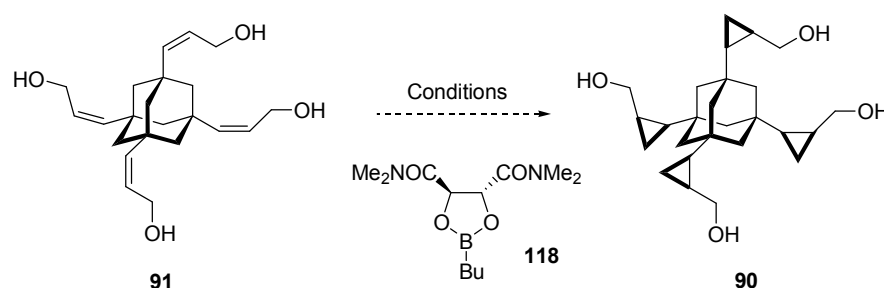
The mechanism of Charetté's improved procedure for the Simmons-Smith cyclopropanation of cinnamyl alcohol (**116**) to cyclopropane **119** in the presence of chiral dioxaborolane ligand **118** is described in Scheme 30. It is clear to us that in the transition state **117**, the boron atom from chiral ligand **118** coordinates with the oxygen in the allylic position of substrate **116**. In addition, zinc coordinates with two oxygen atoms (one allylic oxygen in substrate **116** and one amide oxygen from the chiral ligand **118**), thus delivering the chirality to the substrate. Based on this fact, we hoped that adding another boron source, for example B(OMe)₃, to the reaction mixture could solve the solubility problem through *in situ* desymmetrisation of substrate **91** by forming a soluble intermediate similar to **120** in the reaction equilibrium (Scheme 30).

Scheme 30. Rational for *in situ* desymmetrisation with B(OMe)₃.



Accordingly, Charette's improved Simmons-Smith cyclopropanation of tetra-ol **91** in the presence of B(OMe)₃ was investigated (Table 2). Disappointingly, cyclopropanation of tetra-(*Z*)-allylic alcohol **91** with the addition of dioxaborolane **118** failed to produce any desired product (Entry 1, Table 2). In addition, adding B(OMe)₃ in either catalytic amount (Entry 2, Table 2) or excess amount (Entry 3, Table 2) also gave no evidence of the desired product **90**.

Table 2. Studies on direct cyclopropanation of tetra-ol **91** by *in situ* desymmetrisation.



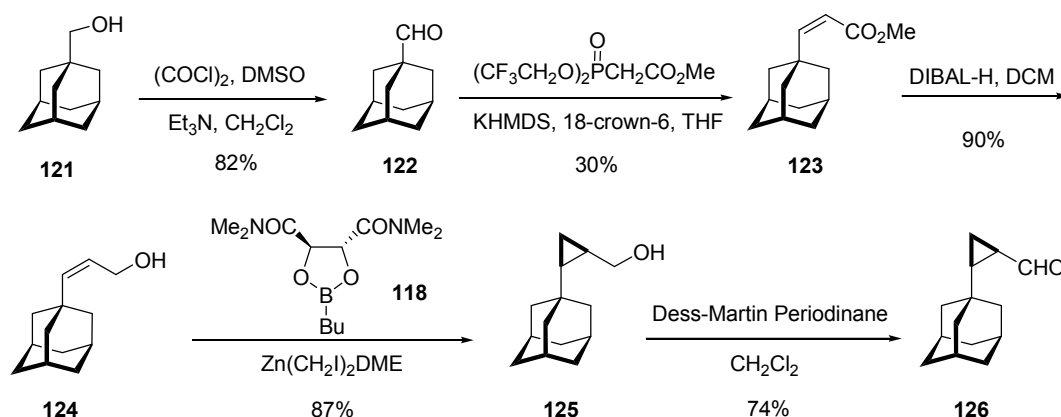
Entry	Reaction Conditions	Results
1	Zn(CH ₂ I) ₂ DME, dioxaborolane 118 , CH ₂ Cl ₂ , -15 °C to r.t., 22 h	No desired product and starting material recovery.
2	Zn(CH ₂ I) ₂ DME, dioxaborolane 118 , CH ₂ Cl ₂ , 0.15 eq. of B(OMe) ₃ , -15 °C to r.t., 22 h	No desired product and starting material recovery.
3	Zn(CH ₂ I) ₂ DME, dioxaborolane 118 , CH ₂ Cl ₂ , excess B(OMe) ₃ , -15 °C to r.t., 6 h	No desired product and starting material recovery.

2.1.2.2. Study on Cyclopropanation of Model Compound **124**

Since direct cyclopropanation of tetra-*cis*-olefin **91** had failed to produce any desired tetra-cyclopropane **90**, attempts were made to study the cyclopropanation of model compound mono-*cis*-olefin **124** (Scheme 31), from which we hoped to find out the reason for the lack of reactivity of the authentic substrate **91** towards cyclopropanation. Thus, Swern oxidation of commercially available 1-adamantanemethanol (**121**) gave rise to aldehyde **122** in 82% yield. The (*Z*)-selective Horner-Emmons olefination of aldehyde **122** under Still-Gennari conditions⁵⁴ provided the desired *cis*-olefin **123** in low yield, owing to

the low solubility of **122** in THF. DIBAL-H reduction of ester **123** to model substrate **124** was achieved in excellent yield. Interestingly, Simmons-Smith cyclopropanation of model compound **124** proceeded smoothly to furnish cyclopropyl alcohol **125** in 87% yield in just two hours. Oxidation of alcohol **125** by Dess-Martin periodinane yielded the corresponding aldehyde **126**.

Scheme 31. Study on cyclopropanation of model compound **124**.



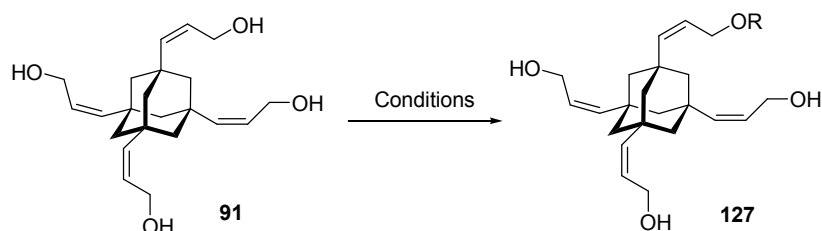
The success of the above model study had demonstrated the feasibility of cyclopropanation of a *cis*-allylic alcohol which is attached to an adamantane moiety. Based on this result, we envisaged that the lack of reactivity of our authentic substrate **91** towards Simmons-Smith cyclopropanation was due to the starting material remaining undissolved in the reaction, or at least insufficiently solvated to allow any significant reaction. Accordingly, the key problem to be solved here was the substrate's solubility in the required solvent CH_2Cl_2 .

2.1.2.3. Synthesis of Tetra-*syn*-cyclopropane **90** by Stepwise Cyclopropanation

We next turned our attention to the stepwise desymmetrisation and cyclopropanation of tetra-*cis*-olefin **91**. Our studies began with the selective protection of one of the four hydroxyl groups in **91** (Table 3). Mono-protection of **91** with Ph_3SiCl using different bases (imidazole, pyridine or KH) produced no desired product **127** (Entries 1, 2 and 3, Table 3).

The use of $^t\text{BuPh}_2\text{SiCl}$ and imidazole was also unsuccessful (Entry 4, Table 3). Pleasingly, we managed to obtain the desired mono-silylated product **127** in 44% yield (66% based on recovered starting material) using $^t\text{BuPh}_2\text{SiCl}$ and DMAP in pyridine at room temperature (Entry 5, Table 3). However, raising reaction temperatures to 50 °C failed to provide the product **127** in a better yield (Entry 6, Table 3). The desymmetrised compound **127** is indeed soluble in CH_2Cl_2 , the solvent required for the following Simmons-Smith cyclopropanation.

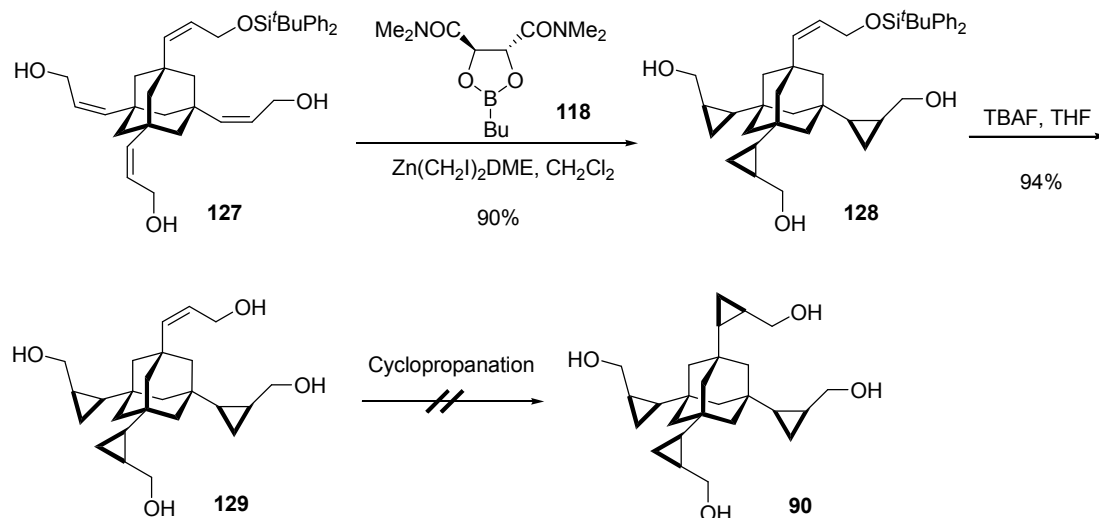
Table 3. Monosilylation of tetra-(*Z*)-allylic alcohol **91**.



Entry	Reaction Conditions	R	Results
1	Ph_3SiCl , ImH, DMF, r.t.	Ph_3Si	no reaction. only 91 recovered.
2	Ph_3SiCl , DMAP, pyridine, r.t.	Ph_3Si	no reaction. only 91 recovered.
3	Ph_3SiCl , KH, 18-crown-6, THF, r.t.	Ph_3Si	no reaction. 91 decomposed.
4	$^t\text{BuPh}_2\text{SiCl}$, ImH, DMF, r.t.	$^t\text{BuPh}_2\text{Si}$	no reaction. 91 decomposed.
5	$^t\text{BuPh}_2\text{SiCl}$, DMAP, pyridine, r.t.	$^t\text{BuPh}_2\text{Si}$	44% yield of 127 and 33% of 91 recovered.
6	$^t\text{BuPh}_2\text{SiCl}$, DMAP, pyridine, 50 °C	$^t\text{BuPh}_2\text{Si}$	35% yield of 127 and 24% of 91 recovered.

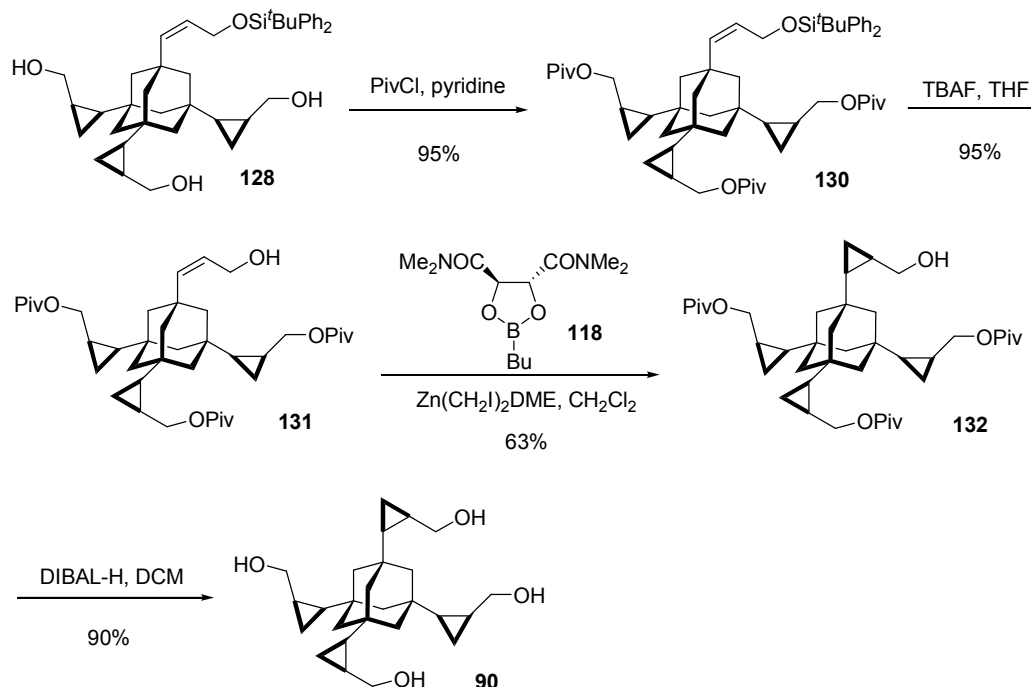
To our delight, Simmons-Smith cyclopropanation of mono-silylated compound **127** using Charette's improved procedure⁵⁷ delivered the desired tri-cyclopropane **128** in excellent yield (Scheme 32). Then, removal of the silyl protecting group with TBAF went smoothly to yield the free allylic alcohol **129** for the final cyclopropanation. Unfortunately, once again compound **129** has low solubility in CH_2Cl_2 . So unsurprisingly, the cyclopropanation of **129** failed to furnish the desired key intermediate tetra-cyclopropane **90**.

Scheme 32. Synthesis of tri-cyclopropane **129**.



The solubility problem associated with **129** was pleasingly solved by following the reaction sequence outlined in Scheme 33. Acylation of all the three free hydroxyl groups in compound **128** with pivalyl chloride in pyridine generated the desired product **130** in almost quantitative yield, which was further desilylated to give the free allylic alcohol **131** in 95% yield. With the CH_2Cl_2 -soluble substrate **131** in hand, we were able to carry out the final Simmons-Smith cyclopropanation to provide the tetra-cyclopropane **132** in good yield. Finally, the key intermediate tetra-*syn*-cyclopropane **90** was obtained in 90% yield by DIBAL-H reduction of the tri-pivalate **132**.

Scheme 33. Synthesis of key intermediate tetra-cyclopropane **90**.



An X-ray crystal structure was desirable in order to unambiguously characterise the key tetra-*syn*-cyclopropane **90**. To our delight, X-ray quality crystals were grown from a 1:1:1 mixture of MeOH, toluene and THF. The graphic representation of the X-ray crystal structure of tetra-*syn*-cyclopropane **90** is shown in Figure 5. Unfortunately, we were unable to define the absolute stereochemistry due to the lack of heavy atoms in the molecule. Perhaps unsurprisingly, the structure is disordered and actually shows an inversion of chirality in one of the four cyclopropyl arms, since the tetra-cyclopropane **90** was constructed sequentially by first tri-cyclopropanation followed by a final cyclopropanation. Figure 5 shows both diastereomers overlapped, while Figure 6 shows X-ray structures of the major diastereomer **90A** (*ca.* 60% occupancy), and the minor diastereomer **90B** (*ca.* 40% occupancy) with each diastereomer possessing greater than 95% optical purity.

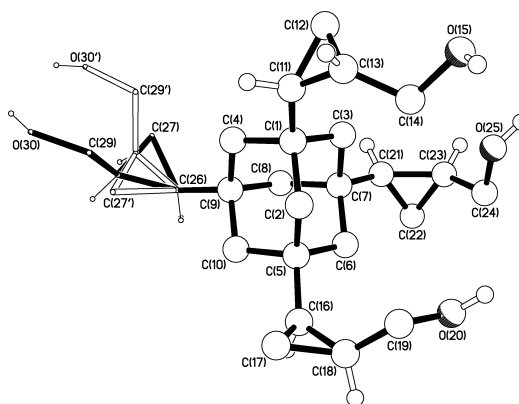


Figure 5. Graphic representation of X-ray crystal structure of tetra-*syn*-cyclopropane **90**.

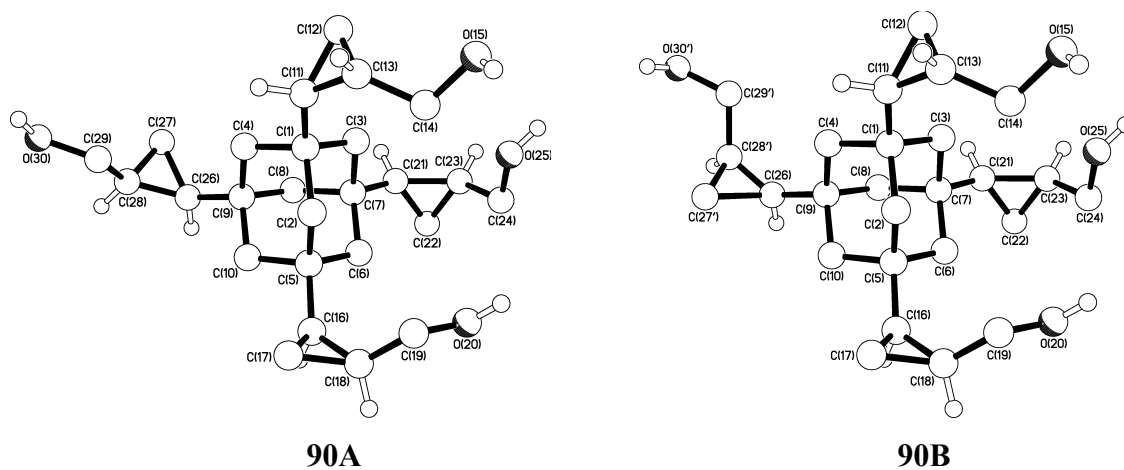
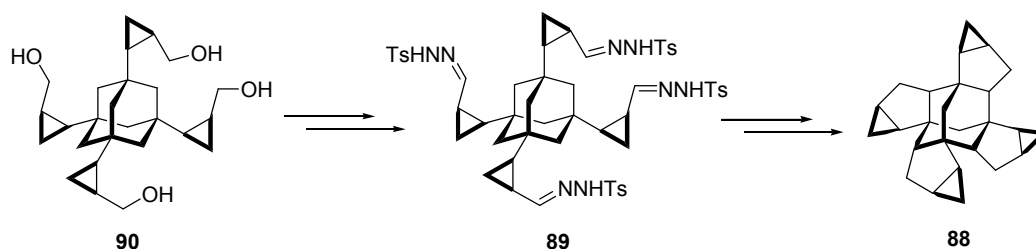


Figure 6. Graphic representations of X-ray crystal structures of two isomers **90A** and **90B** of tetra-*syn*-cyclopropyl alcohol **90**.

2.1.3. Attempted Synthesis of Rearrangement Precursor **88**

Having successfully synthesised the key intermediate tetra-*syn*-cyclopropane **90**, we next, as planned, carried out the synthesis of tetra-hydrazone **89** and its carbene generation (Bamford-Stevens reaction) followed by insertion to rearrangement precursor **88** (Scheme 34).

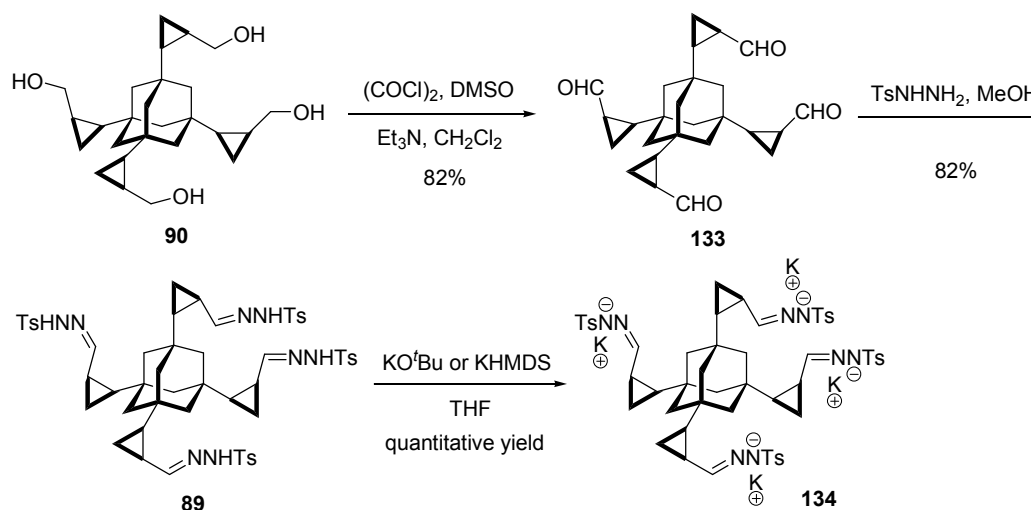
Scheme 34. Planned synthesis of rearrangement precursor **88** from tetra-cyclopropane **90**.



2.1.3.1. Synthesis of Potassium Salt of Tetra-hydrazone **89**

Once again, due to the low solubility of tetra-ol **90** in the solvent of DCM, Swern oxidation of **90** was carried out in the mixed solvents (DMSO/DCM, 2:1) to give the corresponding tetra-aldehyde **133** in 82% yield (Scheme 35). Condensation of *p*-toluenesulfonylhydrazine and tetra-aldehyde **133** provided the desired tetra-tosylhydrazone **89** in good yield after purification by chromatography. Then synthesis of the corresponding tetra-potassium salt **134** was achieved in quantitative yield by treating the tosylhydrazone **89** with either potassium *tert*-butoxide or KHMDS. The identity of potassium salt **134** was confirmed by the solid-state IR, which in both cases (KO^{*t*}Bu and KHMDS) gave identical spectra. Strong evidence for the formation of potassium salt **134** was seen in the shift of the sulfone stretch from 1332 and 1162 cm⁻¹ in tetra-tosylhydrazone **89** to 1228 and 1126 cm⁻¹ in the corresponding tetra-potassium salt **134**.

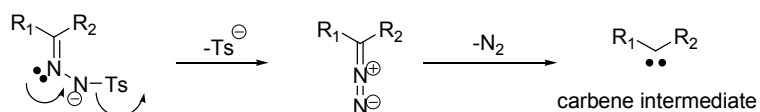
Scheme 35. Synthesis of the potassium salt of tetra-hydrazone **89**.



2.1.3.2. Attempted Carbene Generation and Insertion of **134**

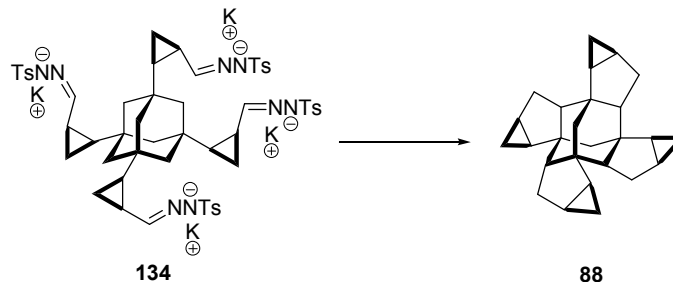
The mechanism of carbene generation from the tosylhydrazone salt is described in Scheme 36, which is similar to the Bamford-Stevens reaction.⁵⁸

Scheme 36. Mechanism for carbene generation from tosylhydrazone salt.



We undertook a limited study of the carbene generation from tetra-potassium salt **134** and its subsequent insertion to construct the polycyclic compound **88**, however under all conditions there was no reaction (Table 4).

Table 4. Attempted carbene generation and carbene insertion of **134**.



Entry	Conditions	Results
1	thermolysis at 138 °C, 2 h	No desired product isolated.
2	BnNEt ₃ Cl, Rh ₂ (OAc) ₄ , 1,4-dioxane, 30 °C, 19 h	No desired product isolated.
3	BnNEt ₃ Cl, Rh ₂ (OAc) ₄ , CH ₂ Cl ₂ , reflux, 18 h	No desired product isolated.
4	Rh ₂ (OAc) ₄ , 18-crown-6, 95 °C, 6 h	Nothing isolated.

We first tried the carbene generation by thermolysis of the potassium salt **134** at 138 °C to provide the carbene insertion product **88** (Entry 1, Table 4). Water was added to the reaction mixture to quench the reaction and hexanes was used for the extraction. Unfortunately, no identifiable organic product was isolated from the reaction mixture. It was thought that the tetra-potassium salt **134** was very stable towards the thermolysis conditions, and was lost in the aqueous layer during work-up with water. As an alternative method to the carbene generation by thermolysis, dirhodium(II) tetraacetate catalysed C-H insertion was next investigated. Inspired by Aggarwal's *in situ* generation of diazo compounds from tosylhydrazone salts in the presence of a phase transfer catalyst⁵⁹, we carried out the carbene insertion reaction of tetra-potassium salt **134** with benzyltriethylammonium chloride and Rh₂(OAc)₄ in both 1,4-dioxane and dichloromethane (Entries 2 and 3, Table 4). However after quenching the reaction with water and extracting with dichloromethane, only a minimal amount of material was isolated and no desired product was observed. To check our work-up procedure, we demonstrated that hexanes was able to extract 85% of adamantane from the mixture of adamantane and 18-crown-6 in water without extracting any 18-crown-6. Thus, we performed the carbene generation and the subsequent insertion of potassium salt **134** in neat 18-crown-6 at 95 °C, at which

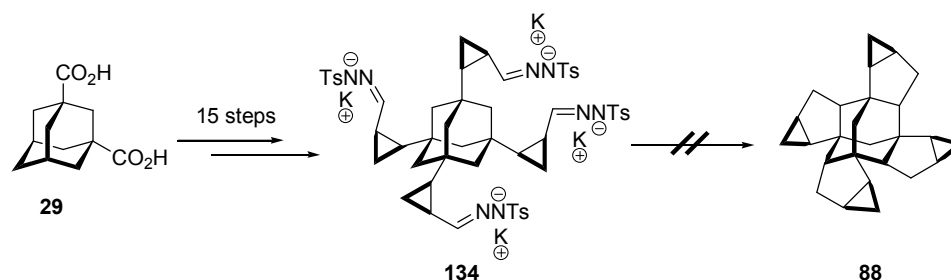
temperature 18-crown-6 is in the liquid form (Entry 4, Table 4). Disappointingly, after quenching the reaction with water, nothing was extracted by hexanes.

The above results indicate that the tetra-potassium salt **134** derived from tetra-tosylhydrazone **89** was unexpectedly stable towards all the conditions that have been investigated. Thus, all of the unreacted tetra-potassium salt **134** was lost in the aqueous layer during work-up.

2.1.4. Conclusions

We have successfully synthesised the tetra-potassium hydrazone salt **134** from the commercially available starting material **29** in 15 steps (Scheme 37). Although the initial plan of building tetra-cyclopropane unit was through a four-directional approach, we encountered solubility difficulties of the cyclopropanation substrate **91** (Table 2). This problem was finally successfully solved by stepwise desymmetrisation of substrate **91**, which has added 5 extra steps to the original proposed synthesis.

Scheme 37. Attempted synthesis of **88** from **29**.



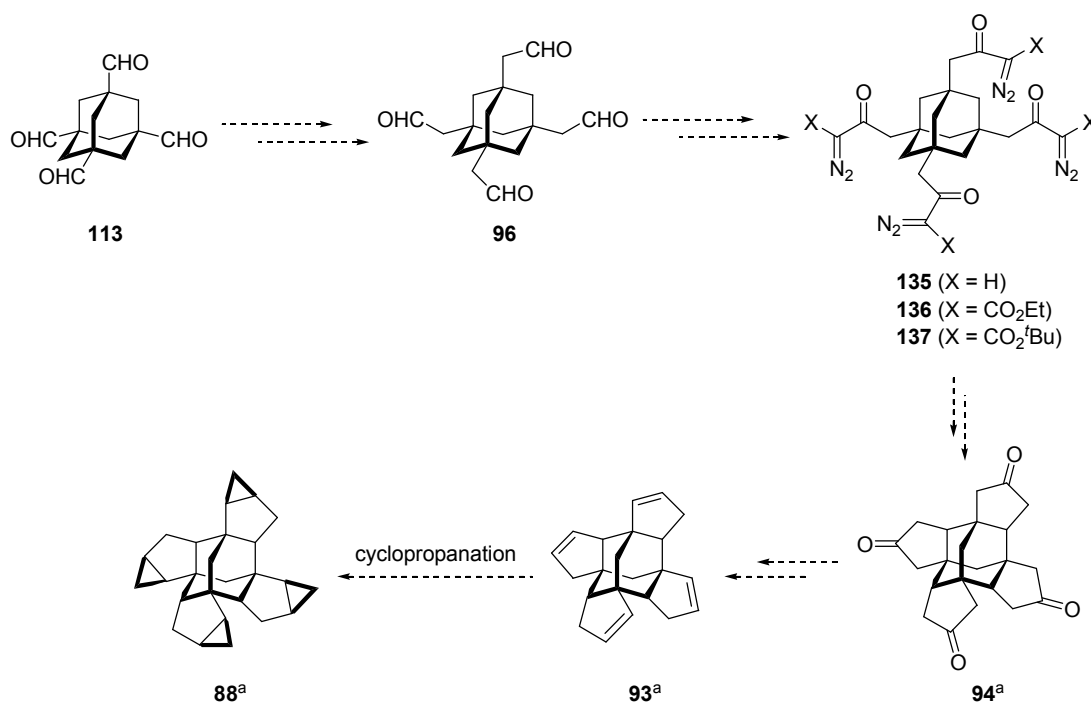
The disappointing part of this synthetic route was the attempt to synthesise hydrocarbon rearrangement precursor **88** *via* tetra-carbene insertion from **134** (Scheme 36). Our limited study on this reaction suggests that the tetra-potassium salt **134** is unexpectedly unreactive towards carbene generation conditions.

As a result of the above facts, we have decided to seek a more promising alternative synthetic route to construct the polycyclic rearrangement precursor **88**. This alternative synthesis (**Route B**) features an early stage tetra-carbene insertion and a late stage tetra-cyclopropanation, in which hopefully the tetra-cyclopropanation substrate will not have the solubility problem. Progress towards **Route B** will be detailed in the following section **2.2**.

2.2. Four-Directional Approach (Route B) to Rearrangement Precursor 88

Since we failed to generate the hydrocarbon rearrangement precursor **88** by **Route A** (section 2.1), we conceived of a new four-directional approach (**Route B**). **Route B** features an early stage tetra-carbene insertion and a late stage tetra-cyclopropanation as outlined in Scheme 38.

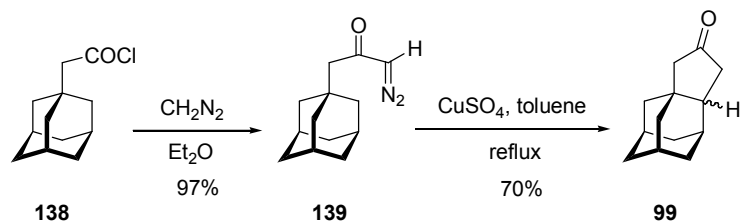
Scheme 38. Proposed four-directional approach (**Route B**) to precursor **88**.



^a The structure shown here is a representative of all possible regio- and stereo-isomers.

In 1970, Chakrabarti⁴³ reported an efficient synthesis of adamantanocyclopentanone **99** from α -keto diazo compound **139**, which was made from the acid chloride **138** and diazomethane (Scheme 39). Based upon this precedent chemistry, we expected that tetra-carbene insertion of tetra-diazo compounds **135**, **136** or **137** may provide the key inserted intermediate in our proposed synthesis of the rearrangement precursor **88** (Scheme 38).

Scheme 39. Literature precedent on carbene insertion of mono-substituted adamantane derivative **139**.



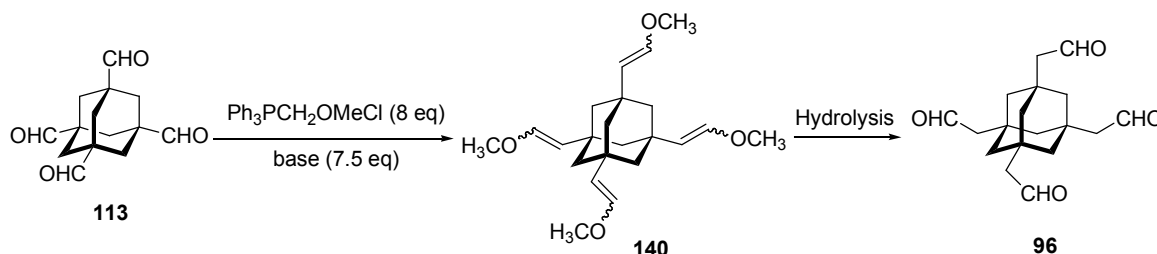
Route B involves a one carbon homologation of the tetra-aldehyde **113** synthesised previously will give the new tetra-aldehyde **96** (Scheme 38). This tetra-aldehyde **96** will then be converted to the tetra-diazo compound (**135**, **136** or **137**), which is expected to undergo tetra-carbene insertion to build the advanced intermediate **94**. We envisaged that the diazo compounds **136** and **137** would be more stable than **135**, since the diazo functional groups are stabilised by two electron-withdrawing groups (a ketone and an ester). In this case, however, compounds **136** and **137** need to undergo an extra step (dealkoxycarbonylation) in order to remove the X group. Reduction of polycyclic tetra-ketone **94** followed by dehydration will generate tetra-olefin **93**, which will then be transformed to the rearrangement precursor **88** by tetra-cyclopropanation, hopefully without any solubility problems encountered with **Route A**.

2.2.1. Attempted Synthesis of Rearrangement Precursor 88 via Tetra-diazo Compound 135

2.2.1.1. Synthesis of Tetra-carboxylic Acid 141

The synthesis of tetra-carboxylic acid **141** began with the one carbon homologation of the known tetra-aldehyde **113**, through a two-step reaction sequence, to form a new tetra-aldehyde **96** (Table 5).

Table 5. Synthesis of tetra-aldehyde **96**.



Entry	1st Step Reaction Conditions	2nd Step Reaction Conditions ^a	Yields
1	LHMDS, -78 to 0 °C, 2 h	acetone/H ₂ O (9:1), HCl, 65 °C, 2 h ^b	16% over 2 steps.
2	LHMDS, -78 to 0 °C, 2 h	acetone/H ₂ O (9:1), HCl, 65 °C, 14 h ^b	14% over 2 steps.
3	NaHMDS, -78 °C to r.t., 16 h	acetone/H ₂ O (9:1), HCl, 65 °C, 3 h ^b	36% over 2 steps.
4	NaHMDS, -78 °C to r.t., 16 h	CF ₃ SO ₃ H, CH ₂ Cl ₂ / <i>i</i> -PrOH/H ₂ O (60:20:1) r.t., 16 h ^c	79% for 1st step; 60% for 2nd step.

^a Reactions were performed at a concentration of 0.02 M.

^b Tetra-enol ethers **140** was taken to the hydrolysis step as a crude product.

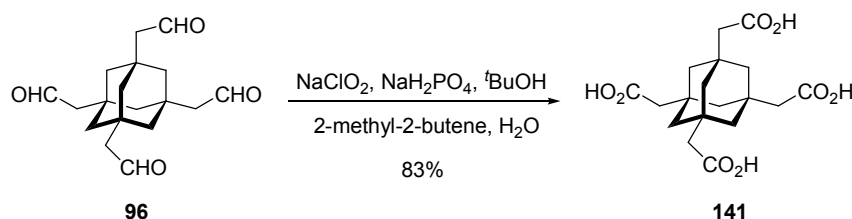
^c Pure tetra-enol ethers **140** was used in the hydrolysis step.

A Wittig reaction of tetra-aldehyde **113** with excess of methoxymethyl-triphenylphosphonium chloride and base (LHMDS) gave tetra-enol ether **140** as a mixture of (*E*)- and (*Z*)-olefins. We first tried the hydrolysis without purification of the Wittig product **140** using HCl in acetone and water (Entry 1, Table 5). However, after flash chromatography purification, it generated an inseparable mixture of the desired tetra-aldehyde **96** and triphenylphosphine oxide, the by-product from the Wittig reaction.

The yield of the desired product **96** was determined to be 16% over two steps by analysing ^1H NMR integrations. Extending the reaction time of the hydrolysis step failed to give any improvement in the overall yield (Entry 2, Table 5). The yield of this two-step reaction sequence was improved to 36% by warming up the Wittig step to room temperature and extending the reaction time to 16 hours (Entry 3, Table 5). In order to better understand the reaction sequence and find out which step accounted for the moderate overall yield, we decided to isolate the intermediate tetra-enol ether **140** after the first step. Thus, **140** was isolated by flash chromatography in 79% yield (Entry 4, Table 5). This time hydrolysis of the pure tetra-enol ether **140** with triflic acid in a mixture of CH_2Cl_2 , *i*-PrOH and H_2O provided the desired tetra-aldehyde **96** in 60% yield (Entry 4, Table 5). Therefore, this two-step procedure gave a better overall yield (48%) by using the pure Wittig product in the hydrolysis step.

The next step was the Pinnick oxidation of the tetra-aldehyde **96**, which went smoothly to furnish the desired tetra-acid **141** in 83% yield (Scheme 40).

Scheme 40. Pinnick oxidation of tetra-aldehyde **96** to tetra-acid **141**.



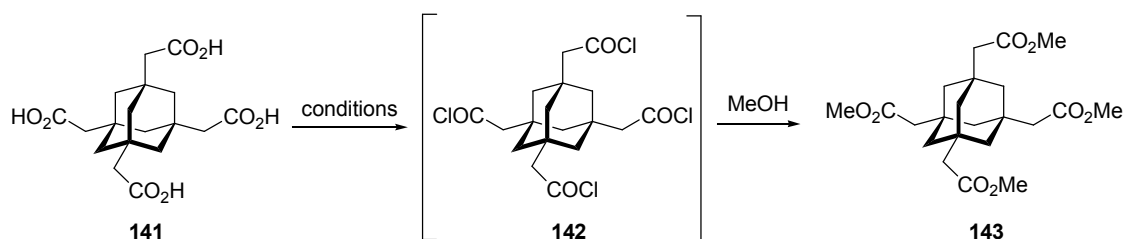
It is noteworthy to mention that the desired tetra-acid **141** is too polar to be purified by normal flash chromatography. Therefore, after the reaction was finished, the acidity of the reaction mixture was adjusted to pH 2 with aqueous HCl. Then the mixture was extracted with EtOAc five times to provide a mixture of the desired compound **141** and other organic impurities. Then, the organic extract was washed with saturated aqueous NaHCO_3 and the product **141** was transformed into its sodium salt and remained in the aqueous phase. This aqueous solution was then reacidified to pH 2 with aqueous HCl. The tetra-acid **141** in the aqueous solution was extracted with EtOAc four times, and after removal of EtOAc under

reduced pressure, the crude product **141** was obtained with great purity and was used in the next step without further purification.

2.2.1.2. Attempted Synthesis of Tetra-diazo Compound **135** from Tetra-acid **141**

Having successfully prepared tetra-acid **141**, we were interested in making tetra-acid chloride **142** (Table 6), which would, upon reaction with diazomethane, provide the desired tetra-diazo ketone **135** (Scheme 38). It seemed impossible to purify the tetra-acid chloride **142** due to its high reactivity towards water. As a result of this, **142** could only be used in the next step as a crude product. Therefore, the intermediate **142** was allowed to react with methanol to yield the tetra-methyl ester **143** as an evidence of the tetra-acid chloride **142** formation. IR was also utilised to detect the characteristic carbonyl absorption of acid chloride functionality in intermediate **142**.

Table 6. Synthesis of tetra-acid chloride **142** from tetra-acid **141**.



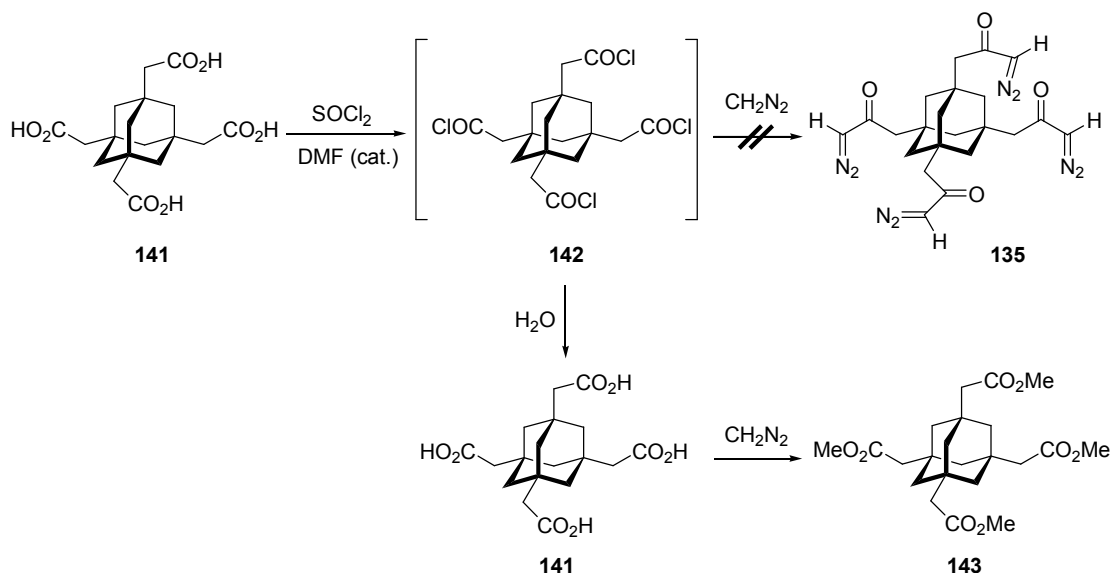
Entry	Conditions	Results
1	SOCl ₂ , reflux, 6 h	Acid chloride carbonyl seen by IR; No 143 formed.
2	SOCl ₂ , reflux, 18 h	Acid chloride carbonyl seen by IR; No 143 formed.
3	(COCl) ₂ , DMF (cat.), CH ₂ Cl ₂ , r.t., 18 h	No acid chloride carbonyl seen by IR.
4	SOCl ₂ , DMF (cat.), CH ₂ Cl ₂ , r.t., 18 h	Acid chloride carbonyl seen by IR; 143 formed in 42% yield over 2 steps.

The tetra-acid **141** has low solubility in most organic solvents, while the corresponding acid chloride **142** is expected to have good solubility. Refluxing tetra-acid **141** in freshly

distilled thionyl chloride generated the acid chloride, as could be seen in the IR spectrum ($\nu(\text{C}=\text{O})$, 1796 cm^{-1}) (Entry 1, Table 6). However, when the crude intermediate was treated with methanol, we failed to observe any desired tetra-methyl ester **143**. This result indicated to us that the tetra-acid chloride formation (Entry 1) was not complete, as no desired product **143** was obtained. It was expected that a complete formation of tetra-acid chloride intermediate **142** would result from increasing the reaction time, but this had little effect (Entry 2, Table 6). Reaction of **141** with oxalyl chloride and catalytic amounts of DMF in CH_2Cl_2 also failed to furnish any desired product **142** (Entry 3, Table 6). Pleasingly, the synthesis of the desired tetra-acid chloride **142** ($\nu(\text{C}=\text{O})$, 1802 cm^{-1}) was achieved by reacting **141** with thionyl chloride and catalytic amounts of DMF in CH_2Cl_2 , as the tetra-methyl ester **143** was obtained in 42% yield over two steps after treating the intermediate **142** with methanol (Entry 4, Table 6).

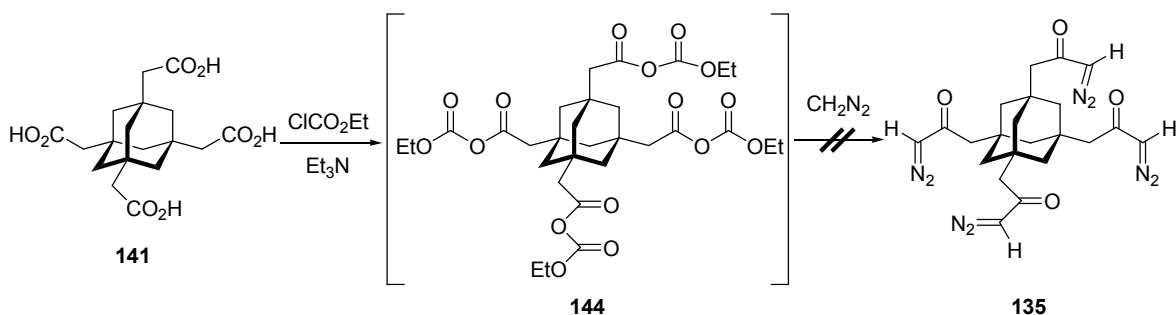
Unfortunately, all attempts at the synthesis of diazo-compound **135** on small scales (20-50 mg) from crude acid chloride **142** and freshly prepared dry diazomethane⁶⁰ were unsuccessful (Scheme 41). Instead, only tetra-methyl ester **143** was isolated from the reaction mixture. This result was not surprising to us, since the tetra-acid chloride intermediate **142** was highly reactive towards the trace amounts of water in the reaction media and hydrolysed to the tetra-acid **141**, which was then reacting with diazomethane to yield tetra-methyl ester **143** only.

Scheme 41. Attempted synthesis of tetra-diazo compound **135** from **142**.



We consequently turned our attention to the use of the mixed anhydride intermediate **144** in this reaction with diazomethane, in a hope that a mixed anhydride would slow down the undesired reaction with water due to its lower reactivity (Scheme 42). The crude mixed anhydride **144** was prepared from tetra-acid **141** with ethyl chloroformate. Unfortunately, reaction of crude **144** with dry diazomethane⁶⁰ failed to produce any desired product **135**, with tetra-methyl ester **143** (Scheme 41) being the only observed product again.

Scheme 42. Attempted synthesis of tetra-diazo compound **135** from **144**.



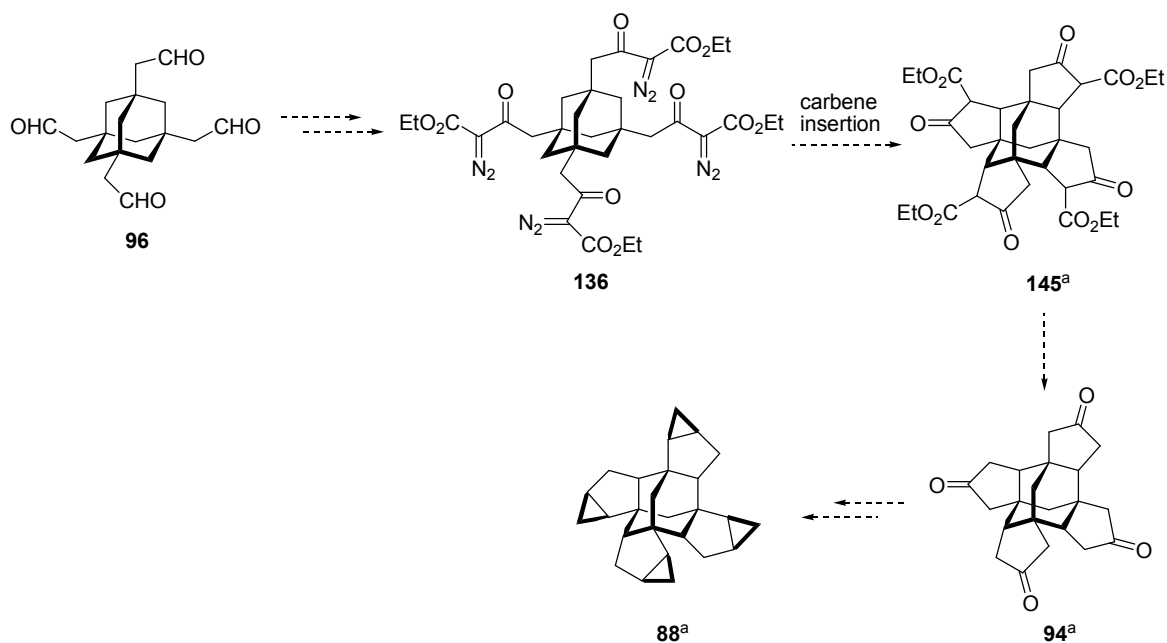
2.2.1.4. Conclusions

The synthesis of tetra-carboxylic acid **141** from tetra-aldehyde **113** was achieved in three steps. Unfortunately, reaction of either acid chloride **142** or mixed anhydride **144** failed to deliver any desired tetra-diazo compound **135**, largely due to the high reactivity of these intermediates towards water. This result prompted us to search for the synthesis of an alternative tetra-diazo compound, such as **136** (Scheme 38). The investigation into the synthesis of tetra-diazo compound **136** and its subsequent carbene insertion reaction will be discussed in the next section.

2.2.2. Attempted Synthesis of Rearrangement Precursor **88** via Tetra-diazo Compound **136**

As we had failed to produce the tetra-diazo compound **135**, we next turned our attention to making the alternative tetra-diazo compound **136** (Scheme 43). It was expected that the tetra-carbene insertion of substrate **136** would lead to the inserted product **145**, which upon dealkoxycarbonylation should furnish the tetra-cyclopentanone **94**.

Scheme 43. Proposed synthesis of rearrangement precursor **88** via tetra-diazo compound **136**.

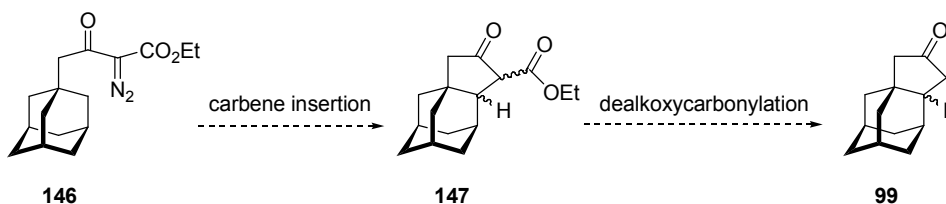


^a The structure shown here is a representative of all possible regio- and stereo-isomers.

2.2.2.1. Model Study

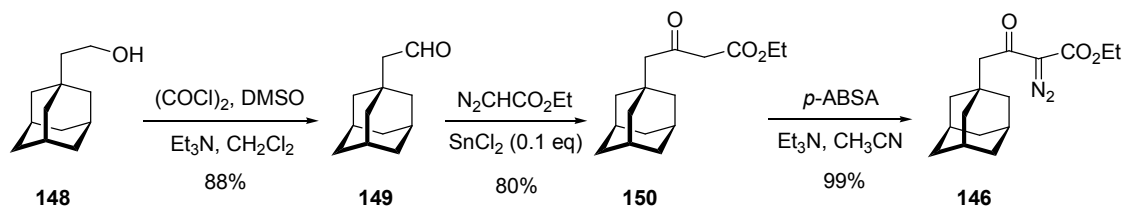
Before we began investigation into the synthesis of the authentic substrate **136** and its subsequent tetra-carbene insertion, we wished to carry out a model study on the mono-substituted adamantane derivative **146** as outlined in Scheme 44. In this model study, we focused on finding optimal reaction conditions for the preparation of substrate **146**, its subsequent carbene insertion and the dealkoxycarbonylation step.

Scheme 44. Proposed model study on mono-substituted adamantane derivative **146**.



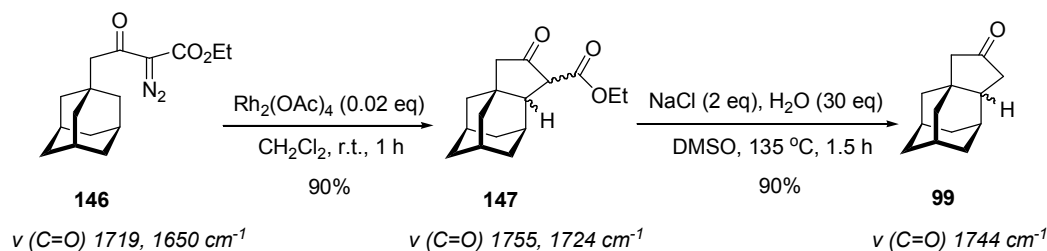
The literature known aldehyde **149** was synthesised from the commercially available material **148** by the Swern oxidation following the literature procedure (Scheme 45).⁶¹ Interestingly, upon standing overnight at room temperature, the aldehyde **149** underwent hydration to give the corresponding hydrated product very easily. Therefore, to improve results, aldehyde **149** was used in the next step immediately after its purification. Thus, treatment of freshly prepared aldehyde **149** with ethyl diazoacetate in the presence of a catalytic amount of SnCl_2 ⁶² smoothly furnished the product **150** as a 4:1 mixture of enol and keto forms. Finally, the Regitz diazo transfer reaction of β -keto ester **150** with *p*-ABSA (*p*-acetamidobenzenesulfonyl azide)⁶³ led to the desired product **146** in quantitative yield.

Scheme 45. Synthesis of the model compound **146**.



With the model α -diazo- β -keto ester **146** in hand, we next set out to examine the key carbene insertion and the following dealkoxycarbonylation reactions. Pleasingly, we found that the transition metal Rh(II) catalysed carbene insertion of the model substrate **146** proceeded smoothly at room temperature to generate the cyclised product **147** in excellent yield (Scheme 46). Although the relative stereochemistry of the two stereo-centres in compound **147** is not important to us as it will be lost in the subsequent step, it is believed that only one diastereomer has been obtained by NMR analysis. Then, the use of Krapcho dealkoxycarbonylation⁶⁴ conditions removed the ethyl ester group from **147**, thus furnishing the desired cyclopentanone **99** in 90% yield. It is interesting to note that the carbonyl absorption in the IR spectrum is very characteristic for this series of transformations. For example, the carbonyl absorptions in compound **147** are 1755 and 1724 cm^{-1} , representing the cyclopentanone ketone and the carbonyl group in the ester, respectively (Scheme 46). After dealkoxycarbonylation, the IR absorption of the cyclopentanone ketone has shifted to 1744 cm^{-1} in compound **99**.

Scheme 46. Carbene insertion and dealkoxycarbonylation of model compound **146**.

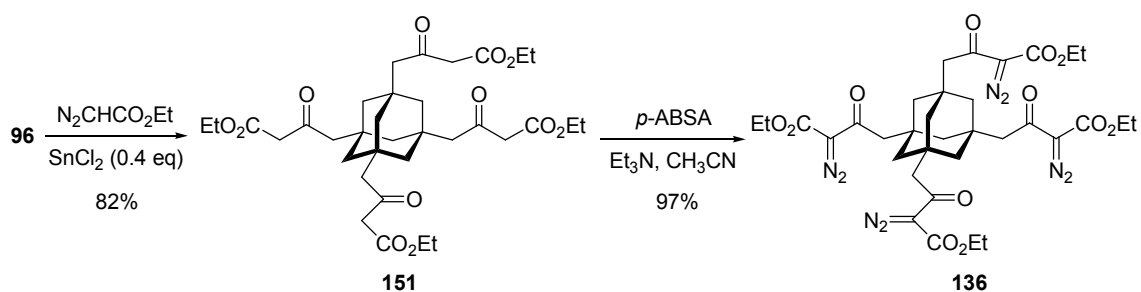


2.2.2.2. Studies on Tetra-carbene Insertion of **136**

Encouraged by the success of our model study on the carbene insertion and the subsequent dealkoxycarbonylation, we decided to examine these reactions on the authentic substrate **136**. Towards this end, the synthesis of tetra-diazo compound **136** from tetra-aldehyde **96** (Scheme 43) was achieved in excellent yield by applying the same reaction sequence that

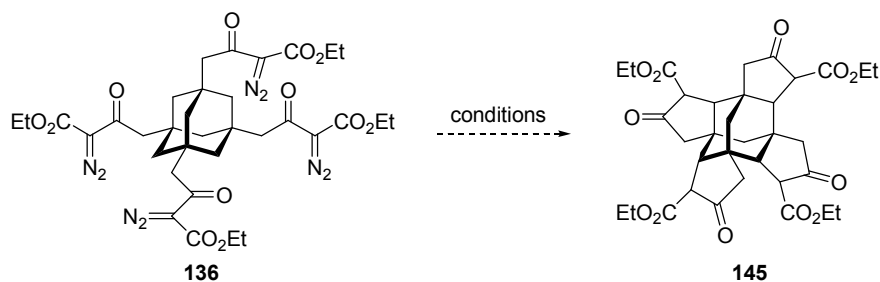
we had developed in our model study (Scheme 47). As we had experienced from the model mono-aldehyde **149**, the tetra-aldehyde **96** was also converted to its hydrated form very quickly. Therefore, tetra-aldehyde **96** was used in the next step immediately after it was prepared in order to obtain the desired product **151** in an improved yield. Interestingly, for the tetra- β -keto ester **151**, the four β -keto ester substituents attached to the adamantane moiety exist exclusively as an all-enol form or an all-keto form (*ca.* 3:1 ratio), rather than as a mixture. The Regitz diazo transfer reaction of tetra- β -keto ester **151** furnished the desired authentic substrate **136** in 97% yield.

Scheme 47. Synthesis of tetra-diazo compound **136** from tetra-aldehyde **96**.



With the authentic substrate **136** in hand, we next investigated the key intramolecular tetra-carbene insertion to the tetra-cyclised product **145** (Table 7). In order to minimise the undesired intermolecular reaction, this step was carried out in a dilute solution (0.01 M). We commenced with applying the same reaction conditions that succeeded in our model study (Entry 1, Table 7). By monitoring the reaction by TLC, starting material **136** disappeared within 1 hour, which indicates that the formation of rhodium carbenoid from diazo compound **136** and $\text{Rh}_2(\text{OAc})_4$ is a very fast process. However, the crude reaction mixture stayed on the bottom line of the TLC even using a polar solvent system (hexanes:EtOAc:MeOH, 1:1:0.2). Thus, no desired product was isolated by flash chromatography.

Table 7. Attempted synthesis of **145** by tetra-carbene insertion of **136**.



Entry	Reaction Conditions ^{a,b}	Results
1	136 in CH ₂ Cl ₂ was added to Rh ₂ (OAc) ₄ in CH ₂ Cl ₂ at r.t., 3 h	no desired product.
2	136 in toluene was added to CuSO ₄ in toluene at r.t., 4 h	no desired product.
3	136 in toluene was added to CuI in toluene at r.t., 2 h	no desired product.
4	136 in toluene was added to CuSO ₄ in refluxing toluene over 2 h	unknown compounds isolated.
5	136 in toluene was added to Rh ₂ (OAc) ₄ in refluxing toluene over 2.5 h	22% of presumed 145 isolated. ^c
6	136 in toluene was added to Rh ₂ (tfa) ₄ in refluxing toluene over 3 h	42% of presumed 145 isolated. ^c
7	136 in toluene was added to Rh ₂ (oct) ₄ in refluxing toluene over 3 h	47% of presumed 145 isolated. ^c
8	136 in toluene was added to Rh ₂ (pfb) ₄ in refluxing toluene over 2 h	25% of presumed 145 isolated. ^c
9	136 in CF ₃ Ph was added to Rh ₂ (tfa) ₄ in refluxing CF ₃ Ph over 2 h	21% of presumed 145 isolated. ^c

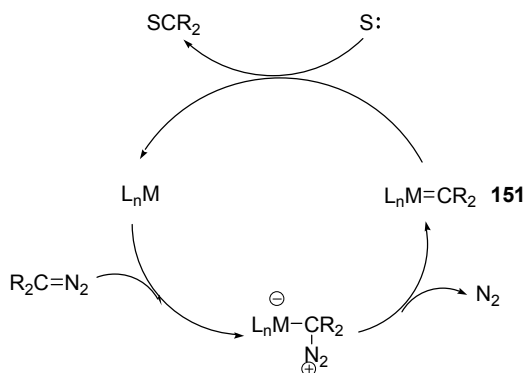
^a All reactions were performed at a concentration of 0.01 M.

^b All reaction were performed by using 0.2 eq of metal catalysts.

^c The identity of the product could only confirmed by IR and ¹H NMR.

As seen in the catalytic cycle of a transition metal catalysed diazo compound decomposition (Scheme 48),⁶⁵ transition metals react as electrophiles with diazo compounds, which causes the loss of dinitrogen and generation of a metal-stablised carbene **151**. Transfer of the carbene entity to an electron-rich substrate completes the catalytic cycle. It is believed that the steric effect plays an important role in the reaction pathway of metal carbenoids.⁶⁶

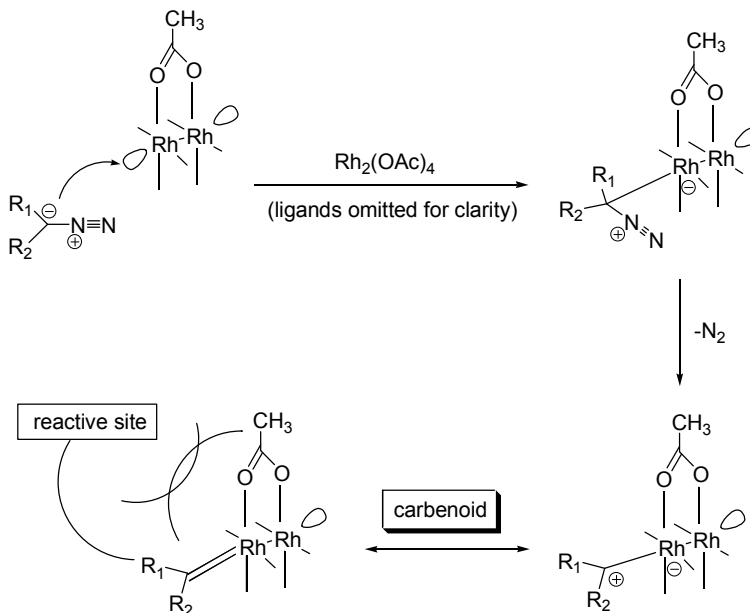
Scheme 48. Catalytic cycle of a transition metal catalysed diazo decomposition.



M: transition metals; L: ligands; S: substrates.

In our case, we envisaged that the rhodium carbenoid formed from $Rh_2(OAc)_4$ was possibly too bulky to undergo intramolecular carbene insertion reaction (Scheme 49).

Scheme 49. $Rh_2(OAc)_4$ catalysed intramolecular carbene insertion.

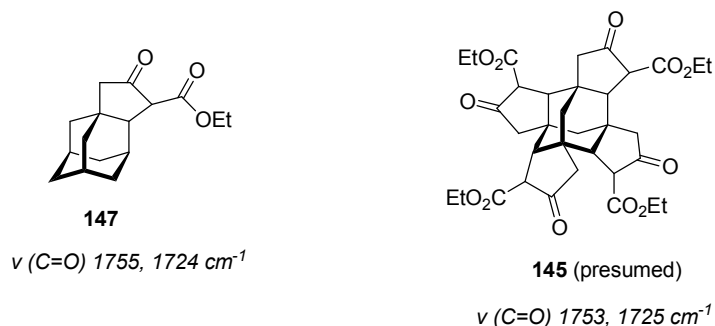


We hoped that by changing the metal source to copper, which has a smaller ligand, for example sulfate or iodide, should give a better result. We also reversed the addition order by adding substrate **136** slowly to the catalyst in toluene, which was expected to minimise

the undesired intermolecular reaction. However, the use of either CuSO₄ or CuI by reverse addition still gave no conversion to the desired product **145** (Entries 2 and 3, Table 7). Raising the temperature only led to the isolation of unknown compounds (Entry 4, Table 7).

Next, we tried the slow addition of the substrate **136** in toluene to a refluxing solution of Rh₂(OAc)₄ in toluene, which resulted in the isolation of several inseparable spots from a very complex mixture (Entry 5, Table 7). The characteristic IR absorptions of carbonyl groups in this mixture of products (1753 and 1725 cm⁻¹) were in good agreement with our model study on the mono-carbene insertion (Scheme 50). This led us to assume that it was the desired product **145**.

Scheme 50. Carbonyl IR absorptions in compounds **147** and **145**.



Unsurprisingly, the ¹H NMR spectrum of this presumed product was not well resolved, owing to the many possible isomers resulting from the tetra-carbene insertion step. Nevertheless, the proton spectrum provided significant evidence for the formation of the desired structure **145** as compared with that of the model compound **147** (Figure 7). However, as we failed to observe the characteristic cyclopentanone carbonyl peak in the ¹³C NMR, we remained uncertain about the identity of this product. In addition, we were unable to detect the correct mass of the desired product **145** from this mixture of material, which led us to be suspicious of the identity of the product.

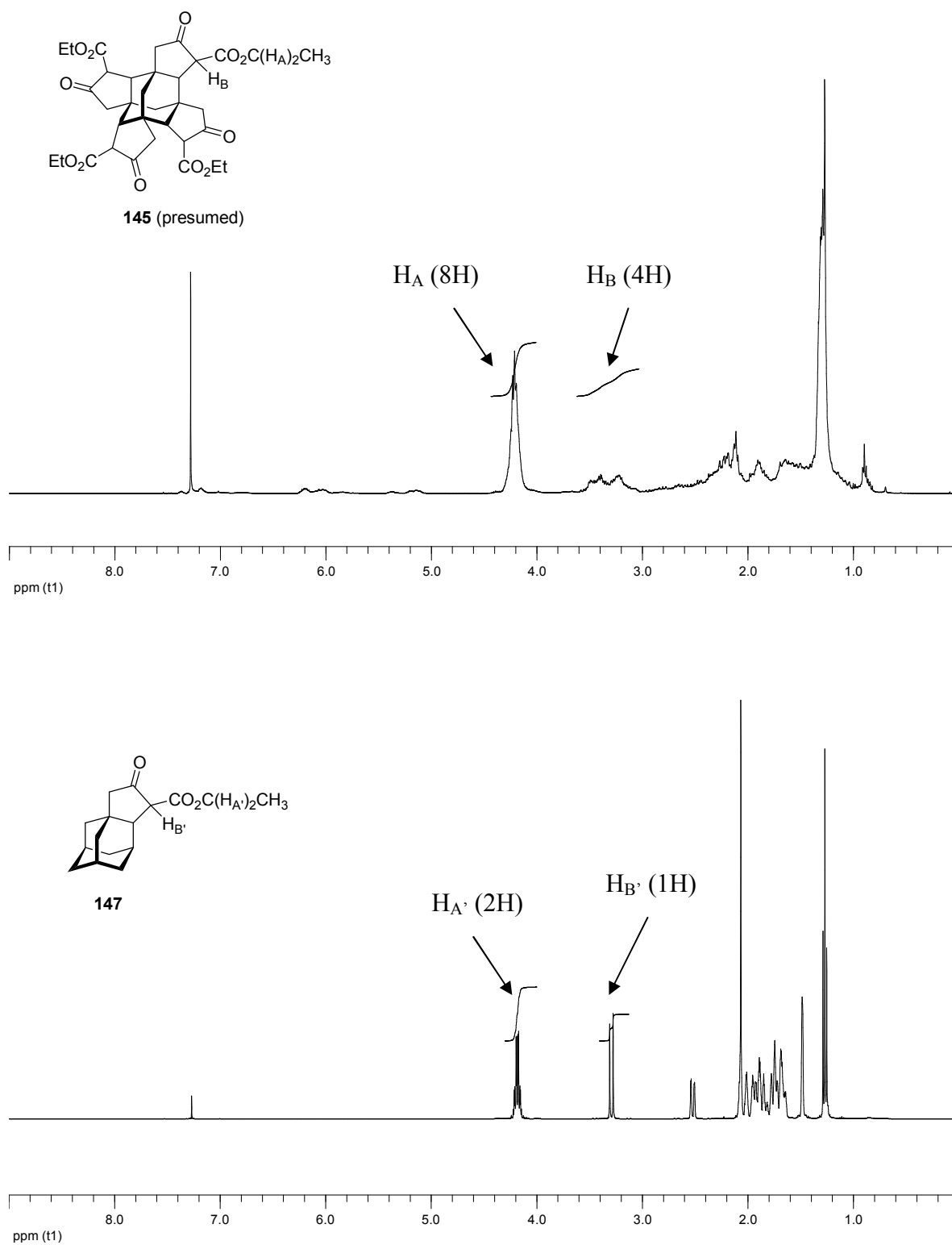
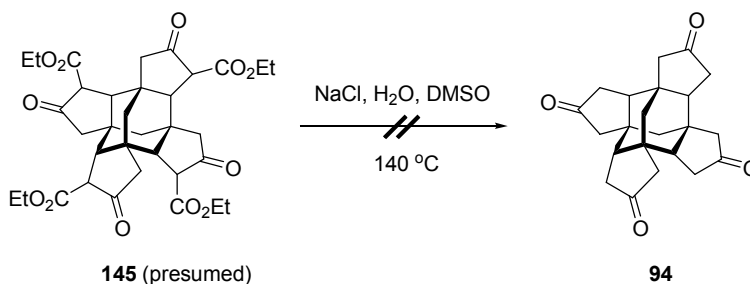


Figure 7. ^1H NMR of the presumed **145** and model compound **147** in CDCl_3 (400 MHz).

It is well-known that the carbene insertion reaction pathways can be controlled by tuning the ligands on the metal.⁶⁷ Thus, among the catalysts screened, Rh₂(tfa)₄ and Rh₂(oct)₄ gave better results (Entries 6, 7 and 8, Table 7), with all the products obtained having the same identity as Entry 5 as discussed above. The use of the catalyst Rh₂(tfa)₄ in α,α,α -trifluorotoluene was also attempted, since the catalyst was expected to have a better solubility in this solvent (Entry 9, Table 7), however, this produced a lower yield of the presumed product **145**.

With encouraging IR and ¹H NMR spectra, we decided to assume the identity of the product as shown for structure **145** (Scheme 51). We envisioned that after elimination of four stereogenic centres in the next step (Krapcho dealkoxycarbonylation), the spectra of the desired product tetra-cyclopentanone **94** would be greatly simplified and more recognizable. Accordingly, the presumed product **145** was subjected to the Krapcho reaction conditions used in our model study (Scheme 46). Unfortunately, this reaction failed to provide the desired product **94**, with only starting material recovery by crude ¹H NMR analysis (Scheme 51).

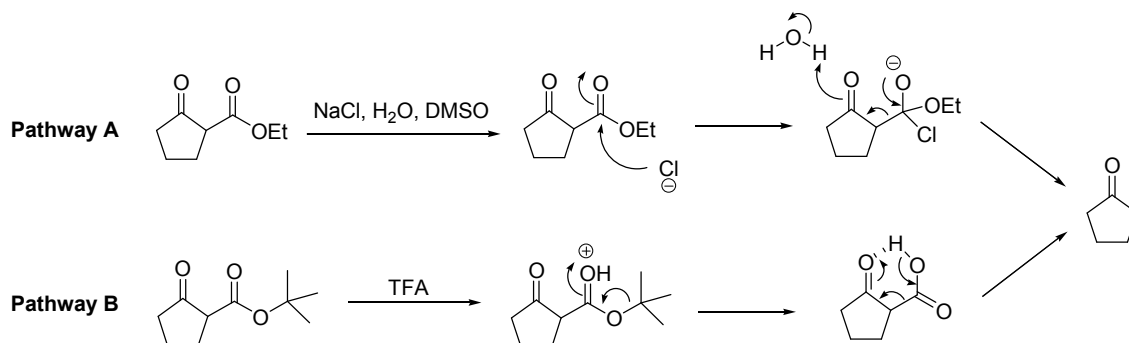
Scheme 51. Attempted synthesis of **94** from presumed **145**.



We reasoned that the failure of this Krapcho reaction was more than likely due to the sterically hindered environment of the ester carbonyl groups, thus inhibiting nucleophilic attack of the chloride ion to the ester carbonyl, which is required as the first step in this dealkoxycarbonylation (**Pathway A**, Scheme 52). To overcome this problem, we decided to use a *tert*-butyl ester as an alternative, as it is known to undergo facile dealkoxycarbonylation upon treatment with TFA. The steric environment should have no

influence on this reaction of *tert*-butyl ester, since the nucleophilic attack on the ester carbonyl groups is not involved in this mechanism (**Pathway B**, Scheme 52). Progress towards this new strategy will be discussed in the next section.

Scheme 52. Mechanisms of dealkoxycarbonylation of ethyl β -keto ester (**Pathway A**) and *tert*-butyl β -keto ester (**Pathway B**).



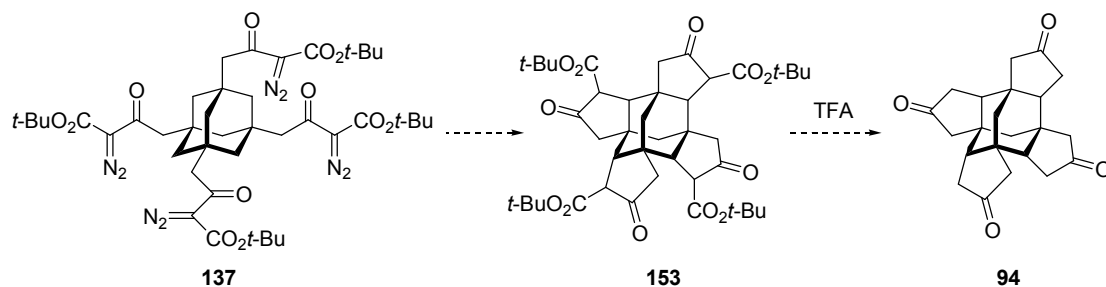
2.2.2.3. Conclusions

The intramolecular carbene insertion of the model compound α -diazo- β -keto ester **146** and the subsequent dealkoxycarbonylation were achieved (Scheme 46). By applying the same synthetic strategy, synthesis of the authentic substrate tetra- α -diazo- β -keto ester **136** was accomplished (Scheme 47). However, considerable investigations into the tetra-carbene insertion of the authentic substrate **136** only led to a production of product **145**, the identity of which could not be fully confirmed (Table 7). It was our hope that the removal of the four ester groups would simplify the structural determination and allow us to confirm the presence of the desired tetra-carbene inserted product **145**. Unfortunately, dealkoxycarbonylation of the presumed product **145** gave no conversion to the desired product **94** (Scheme 51).

It was at this juncture, we decided to turn our attention to an alternative tetra-carbene insertion substrate tetra-*tert*-butyl ester **137** (Scheme 53), since the inserted product **153** was expected to undergo dealkoxycarbonylation smoothly in the presence of TFA without

the steric hindrance effects encountered with the presumed tetra-ethyl ester **145**. The studies towards this new strategy will be discussed in detail in the following section.

Scheme 53. Proposed synthesis of tetra-cyclopentanone **94** from tetra-diazo compound **137**.

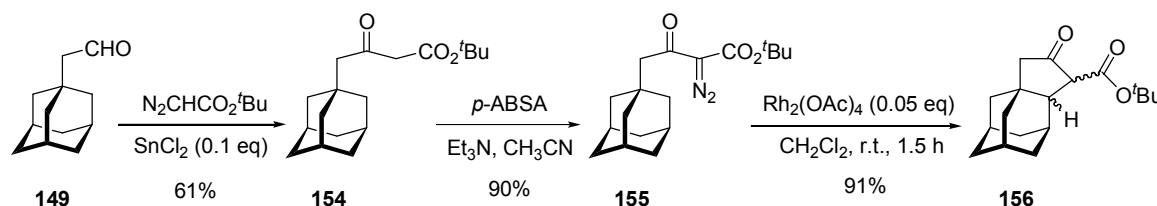


2.2.3. Towards the Synthesis of Rearrangement Precursor **88** via Tetra-diazo Compound **137**

2.2.3.1. Model Study

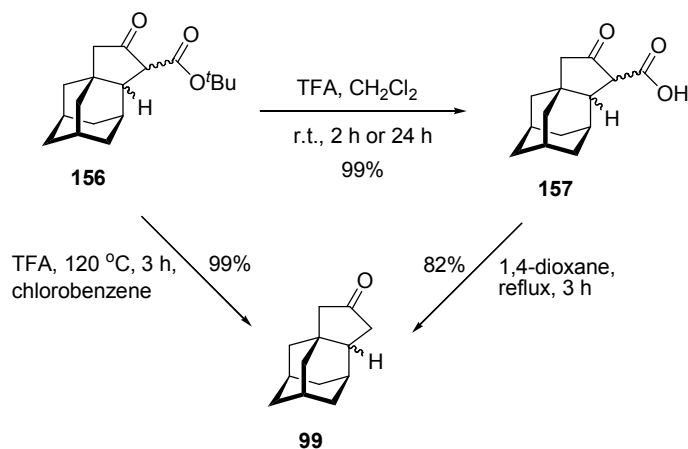
We commenced with a model study on the synthesis of *tert*-butyl derivative **156** and its subsequent dealkoxycarbonylation. By using the same synthetic strategy we developed previously, the *tert*-butyl ester **156** was prepared from aldehyde **149** in excellent overall yield (Scheme 54).

Scheme 54. Synthesis of **156** from the aldehyde **149**.



With the model compound **156** in hand, we next carried out its dealkoxycarbonylation with trifluoroacetic acid. Stirring of **156** with TFA at room temperature for either 2 hours or 24 hours only led to the removal of the *tert*-butyl group, thus providing the β -keto acid **157** in quantitative yield (Scheme 55). Then, decarboxylation of the isolated intermediate β -keto acid **157** in refluxing dioxane gave the desired cyclopentanone **99** in good yield. The suggested mechanism for this transformation proceeds *via* a six-membered ring transition state, as shown in Scheme 52 (**Pathway B**). This result indicated to us that although the removal of *tert*-butyl groups with TFA was a facile reaction, the decarboxylation of intermediate **157** required higher energy. Indeed, treatment of **156** with TFA in chlorobenzene at 120 °C for 3 hours allowed us to isolate the desired decarboxylated product **99** in one step and in quantitative yield.

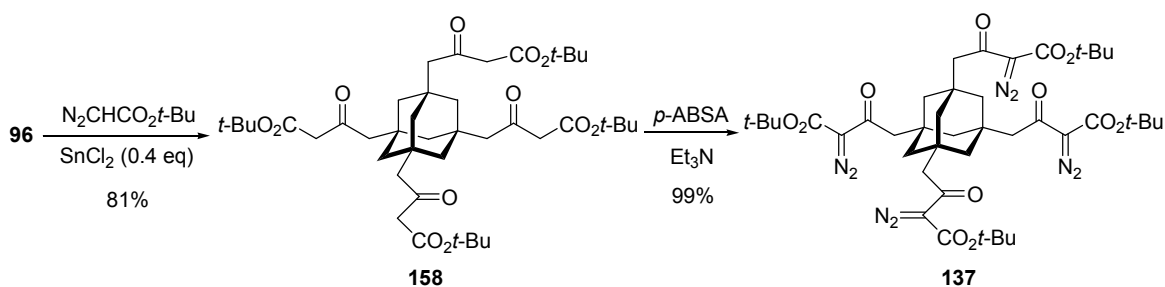
Scheme 55. Dealkoxycarbonylation of *tert*-butyl β -keto ester **156**.



2.2.3.2. Studies on Tetra-carbene Insertion of **137**

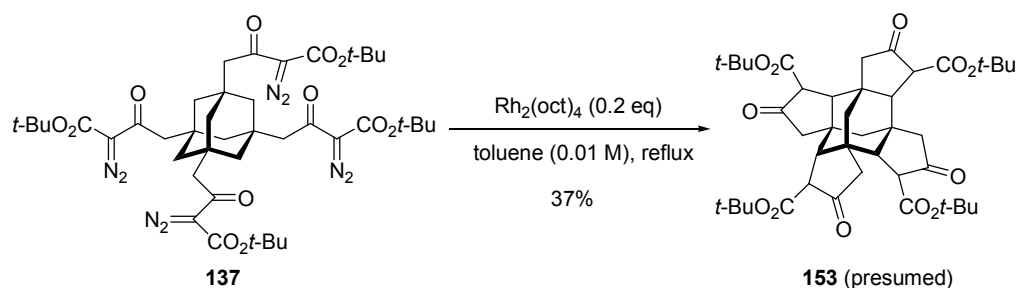
Encouraged by the success of our model study on the carbene insertion and the subsequent dealkoxycarbonylation with TFA, we next examined these reactions on the authentic substrate **137**. Towards this end, the synthesis of tetra-diazo compound **137** from tetra-aldehyde **96** was achieved in excellent yield, by applying the same reaction sequence used previously (Scheme 56). Interestingly, as in the case of compound **152** (Scheme 48), the tetra- β -keto ester **158** also exists as either an all-enol form or an all-keto form (*ca.* 4:1 ratio), rather than a mixture.

Scheme 56. Synthesis of tetra- α -diazo- β -keto ester **137**.



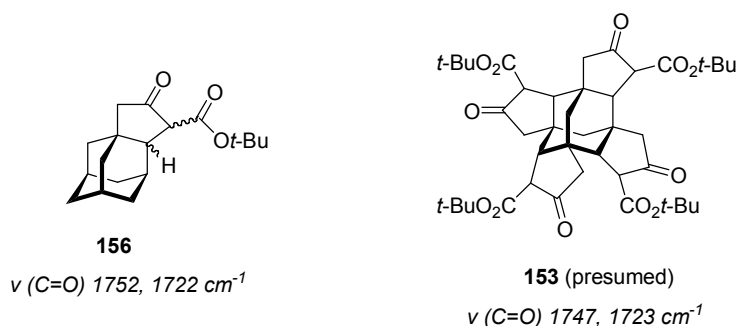
With the authentic substrate **137** in hand, we then attempted the tetra-carbene insertion of substrate **137** by adopting the best catalyst ($\text{Rh}_2(\text{oct})_4$) screened in our previous studies (Table 7). Thus, slow addition of substrate **137** in toluene *via* a syringe pump to a refluxing solution of the catalyst in toluene produced product **153** in 37% yield (Scheme 57). As in the case of the presumed tetra-carbene insertion product **145**, the identity of **153** could only be confirmed by IR and ^1H NMR to some extent, but not by other analytical techniques.

Scheme 57. Tetra-carbene insertion of **137** to the presumed **153**.



The IR carbonyl absorptions in the presumed product **153** (1747 and 1723 cm^{-1}) matched the inserted product **156** (1752 and 1722 cm^{-1}) in our model study (Scheme 58).

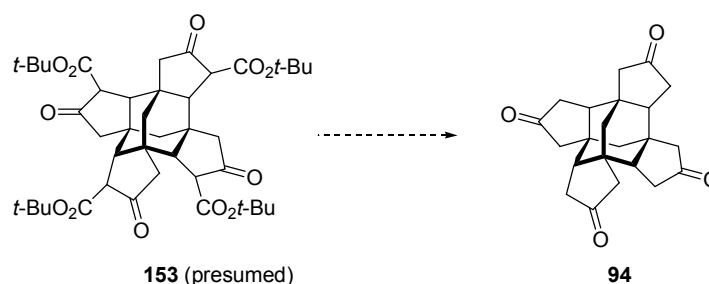
Scheme 58. Carbonyl IR absorptions in compounds **156** and presumed **153**.



As already noted in section 2.2.2, we anticipated that removal of the four *tert*-butyl ester groups would simplify the structure by eliminating four stereogenic centres. Therefore, we attempted the tetra-dealkoxycarbonylation of the presumed **153** to the tetra-cyclopentanone **94**. Table 8 summarises our results. Disappointingly, under no reaction conditions was the

desired product **94** observed by IR or ^1H NMR analysis. Nevertheless, we observed the removal of four *tert*-butyl groups when the presumed **153** was treated with TFA at room temperature for 5 hours by checking the ^1H NMR of the crude product (Entry 1, Table 8). However, when the presumed **153** was reacted with TFA in chlorobenzene at 120 °C, conditions that worked nicely for our model system (Scheme 55), no desired product **94** was isolated (Entry 4, Table 8).

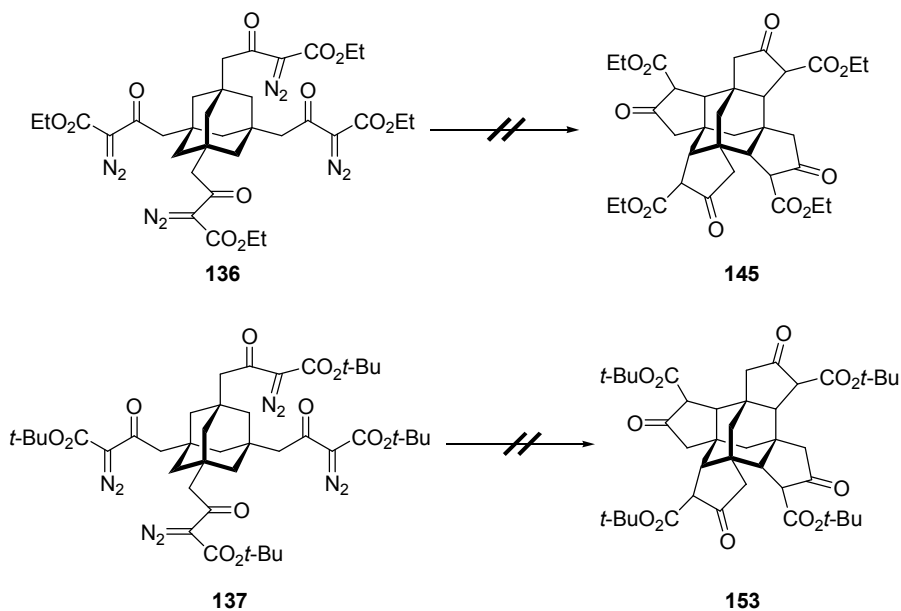
Table 8. Attempted synthesis of **94** from the presumed **153**.



Entry	Reaction Conditions	Results
1	TFA, CH_2Cl_2 , r.t., 5 h	<i>Tert</i> -butyl groups disappeared. No desired product.
2	HCl, dioxane, r.t., 24 h	No desired product isolated from aqueous work-up.
3	TFA, CH_2Cl_2 , reflux, 2 h	No desired product isolated from aqueous work-up.
4	TFA, chlorobenzene, 120 °C, 4 h	No desired product isolated.

Considering the ease of dealkoxycarbonylation with TFA for our model compound **156** and the fact that the presumed **153** was not able to be confirmed by analytical techniques except IR, at this stage it became clear that we were unsuccessful in producing the tetra-carbene inserted products **145** and **153** (Scheme 59). By comparison with our model study, it was thought that the failure of this tetra-carbene insertion reaction was possibly due to the steric hindrance inherent in having four substituents attached to the adamantane moiety in the substrates **136** and **137**. In addition, the failure was also attributed to the fact that the reactive rhodium carbenoid species, formed from Rh(II) and diazo compound, could undergo some undesired reactions rather than C-H insertion, for example, ylide formation and rearrangement.⁶⁷

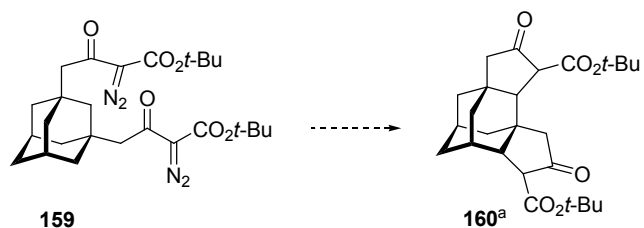
Scheme 59. Attempted syntheses of tetra-carbene inserted products **145** and **153**.



2.2.3.3. Model Study on Di-carbene Insertion of **159**

In order to find out the reasons that accounted for the failure of tetra-carbene insertion of substrates **136** and **137**, we wished to demonstrate the feasibility of di-carbene insertion of the substrate **159** to the cyclised product **160** (Scheme 60).

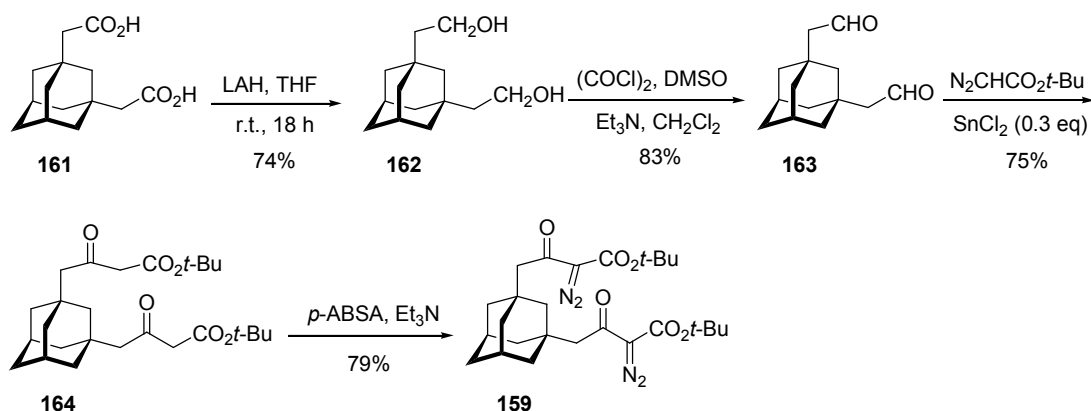
Scheme 60. Proposed di-carbene insertion of **159** to **160**.



^a The structure shown here is a representative of all possible regio- and stereo-isomers.

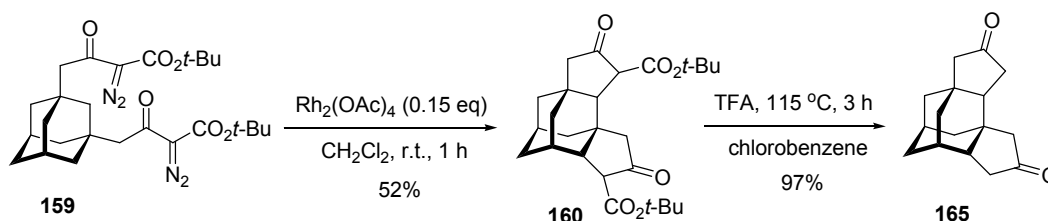
To this end, the commercially available di-carboxylic acid **161** was reduced to the corresponding di-ol **162**⁶⁸ in good yield using lithium aluminium hydride (Scheme 61). Swern oxidation of di-ol **162** smoothly furnished the di-aldehyde **163**, which was then reacted with *tert*-butyl diazoacetate to give the di- β -keto ester **164** in 75% yield. The Regitz diazo transfer reaction converted **164** to the desired diazo compound **159**.

Scheme 61. Synthesis of di- α -diazo- β -keto ester **159**.



Pleasingly, the di-carbene insertion of **159** in the presence of $\text{Rh}_2(\text{OAc})_4$ gave the desired cyclised product **160** in 52% yield along with some unknown by-products (Scheme 62). Then, dealkoxycarbonylation of **160** with TFA in chlorobenzene at 115 °C proceeded smoothly in just 3 hours to furnish the di-cyclopentanone **165** in almost quantitative yield.

Scheme 62. Di-carbene insertion of **159** and the subsequent dealkoxycarbonylation.



It should be noted that there are many possible stereo- and regio-isomers arising from the dicarbene insertion of **159**. The two possible regio-isomers (*syn*-**160** and *anti*-**160**) in

Figure 8 represent the relative relationship between the two cyclopentanone units. For simplicity sake, structure **160** is used to represent the many possible isomers from the di-carbene insertion. The same rule applies to the dealkoxycarbonylation product **165**.

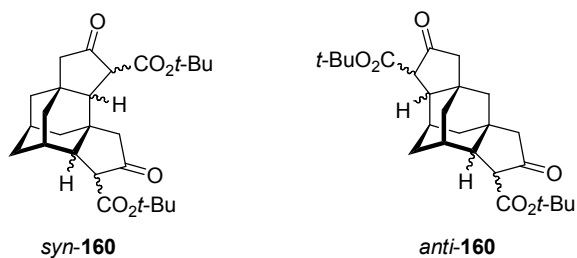


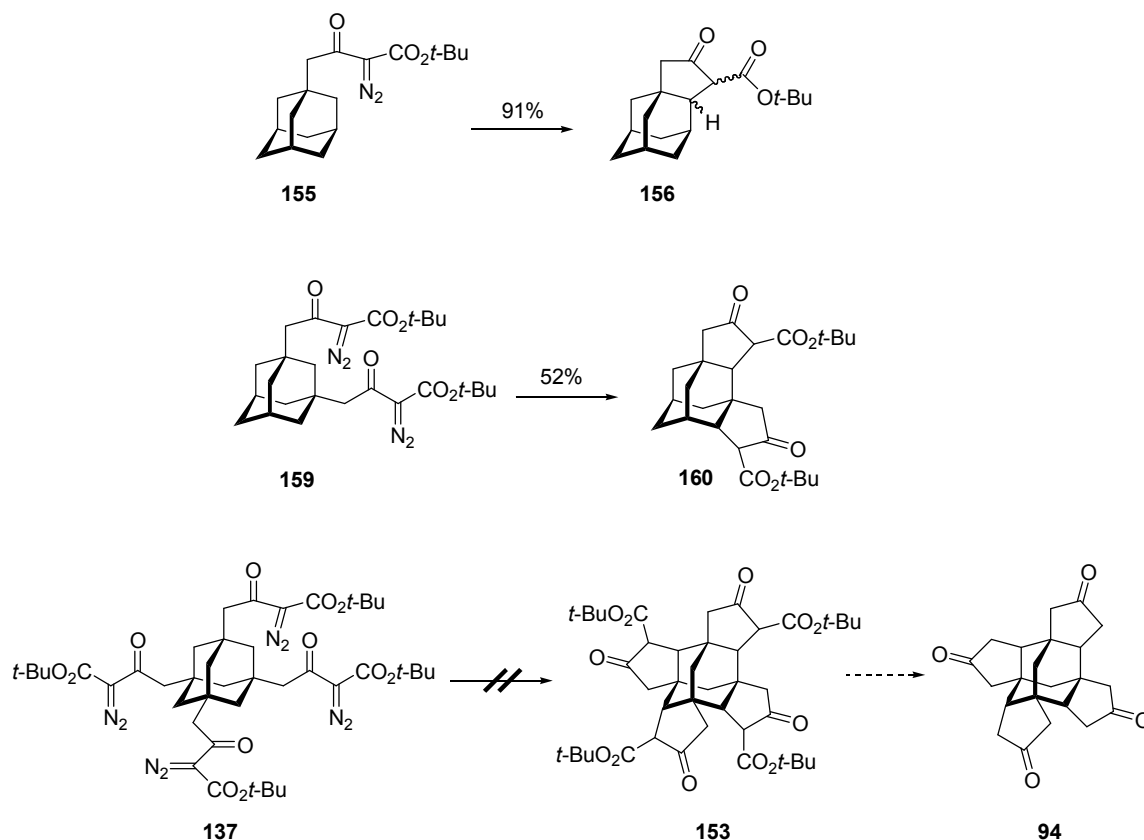
Figure 8. Possible products from di-carbene insertion of **159**.

2.2.4. General Conclusions and Future Work

2.2.4.1. General Conclusions

The above discussion details our efforts towards the synthesis of the key intermediate **94** (Scheme 63). Our synthetic approach relies on the tetra-carbene insertion of the substrate **137**. Accordingly, model studies on mono-carbene insertion and di-carbene insertion were carried out successfully.

Scheme 63. Studies on mono-, di- and tetra-carbene insertions.



We have developed synthetic strategies that allow us to access the carbene insertion substrates **155**, **159** and **137** (Scheme 63) in good yields from the commercially available starting materials. Whilst the mono-carbene insertion of **155** furnished the desired product **156** in excellent yield, the di-carbene insertion of **159** led to the product **160** in only

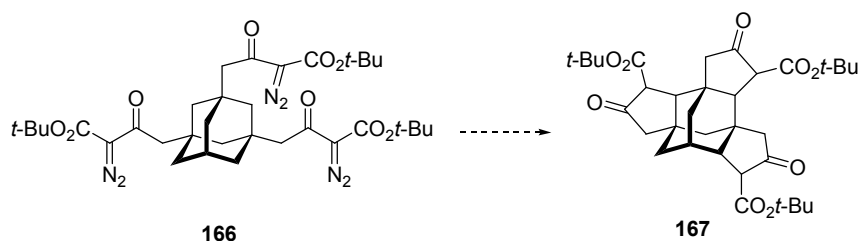
moderate yield due to the generation of some unknown by-products. Although considerable time was spent on the tetra-carbene insertion of the authentic substrate **137**, no desired product **153** was isolated.

Owing to time constraints it was not possible to investigate this strategy further. However, considering the facts that the model mono-carbene and di-carbene insertions have been successful, the tetra-carbene insertion of **137** to the cyclised product **153** still remains a highly interesting and promising synthetic approach. A more detailed investigation into catalysts and reaction conditions would be required to advance this study. It is anticipated the tetra-carbene insertion would ultimately permit the access to the product **153**, although possibly in a low yield, which is a common problem for a multi-directional synthesis.

2.2.4.2. Future Work

For future work along this synthetic strategy, it would be of great interest to investigate the tri-carbene insertion of substrate **166** described in Scheme 64. A study on this model system would allow us to further understand the reactivity of our authentic tetra-carbene insertion (**137** $\rightarrow$ **153**, Scheme 63).

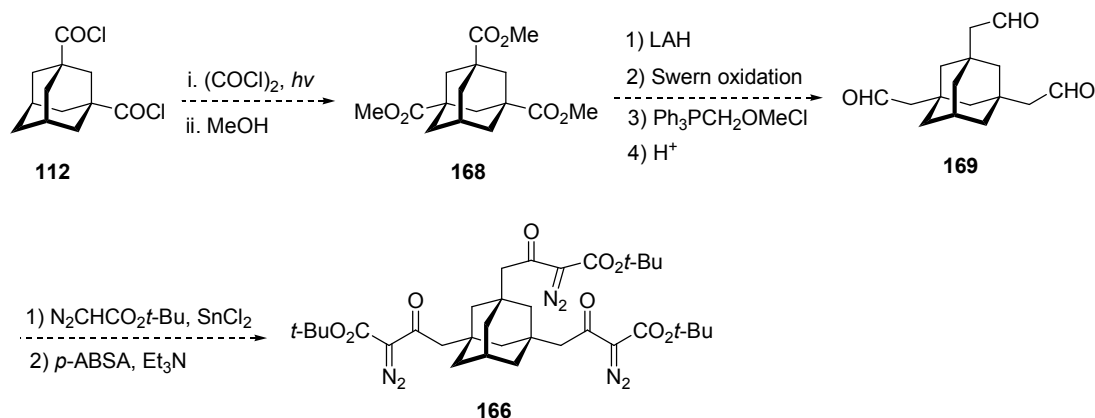
Scheme 64. Proposed tri-carbene insertion of **166** to **167**.



Consequently, the tri-carbene insertion substrate **166** would be prepared from the tri-methyl ester **168** by applying the reaction sequence that we have developed in our previous studies (Scheme 65). As already noted in section 2.1.1.3, a tri-substituted adamantane derivative is an intermediate in the photocarbonylation of 1,3-adamantanedicarbonyl chloride (**112**).

Therefore, by careful monitoring of this photochemical reaction process, we should be able to obtain the tri-methyl ester **168** as a major product after treatment of the crude product with methanol.

Scheme 65. Proposed synthesis of **166** from di-acid chloride **112**.

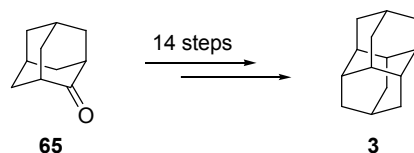


With the successful model studies described in this section, it would also be worth investigating the syntheses of the lower diamondoid hydrocarbons (diamantane (**3**), triamantane (**4**) and tetramantanes (**5**, **6**, **7**)) (Figure 1), in light of a rational design of the rearrangement precursors. Our design, compared to that of the previous approaches in the literature (see section 1.2), could provide a novel and general route to these diamondoids.

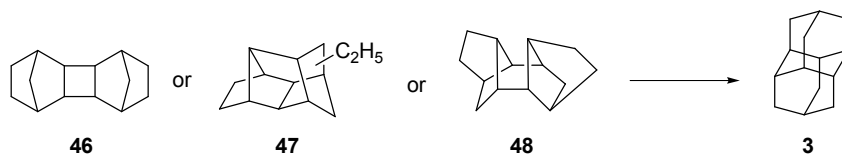
In the case of diamantane (**3**), as we have discussed in section 1.2, two synthetic approaches have been developed in the literature, however both have disadvantages (Scheme 66). The stepwise synthesis (**Approach A**) involves a high number of steps (14 steps from compound **65**). In the second route (**Approach B**), the synthesis of rearrangement precursors **46**, **47** and **48** shows less generality in the structural design.

Scheme 66. Syntheses of diamantane (**3**) in literature.

Approach A: Stepwise synthesis of diamantane (**3**) from **65**.

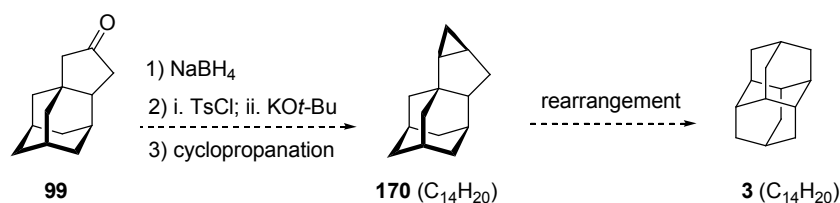


Approach B: Synthesis of diamantane (**3**) via rearrangement of hydrocarbon precursors.



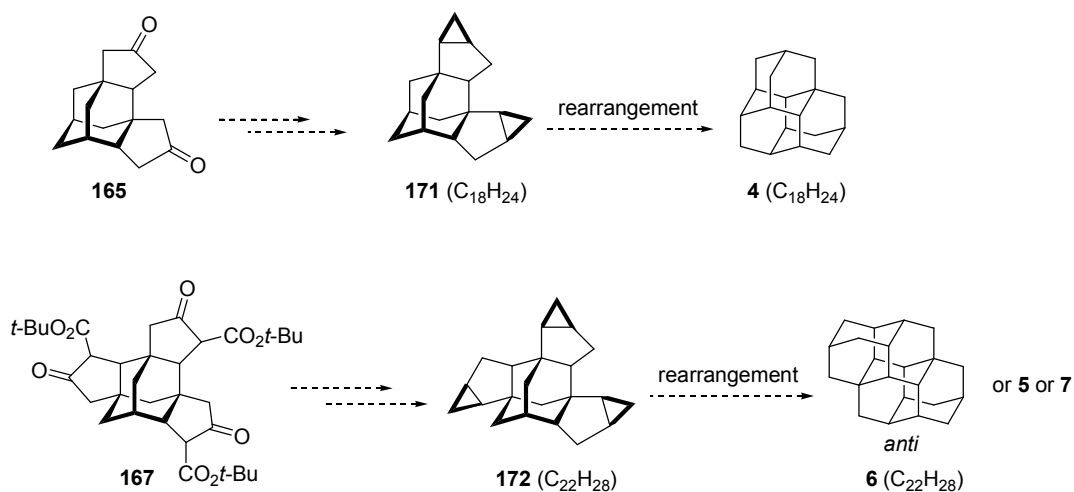
Our proposed rearrangement precursor **170** ($\text{C}_{14}\text{H}_{20}$) to diamantane (**3**) would be synthesised from the known mono-cyclopentanone **99** in a three-step procedure (Scheme 67). Hydrocarbon **170** ($\text{C}_{14}\text{H}_{20}$) is then expected to rearrange to diamantane (**3**) ($\text{C}_{14}\text{H}_{20}$) under acidic conditions. Of course careful choice of Lewis acid or superacid is crucial to the success of the rearrangement, which has been extensively studied in the literature and briefly discussed in the section 1.2 of this thesis.

Scheme 67. Proposed synthesis of rearrangement precursor **170** to diamantane (**3**).



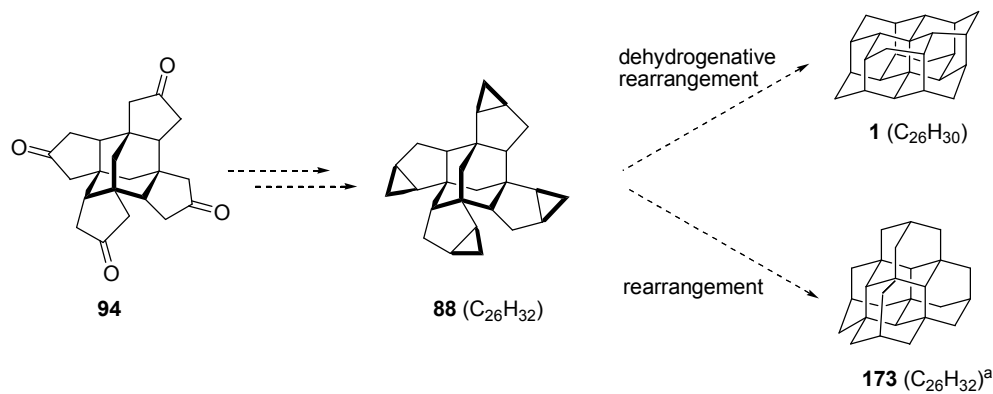
This approach, should it be successful, would allow us to be confident of a novel and general design of the hydrocarbon rearrangement precursors to triamantane (**4**) and tetramantanes (**5**, **6** or **7**) (Scheme 68). The precursors **171** and **172** to these diamondoid hydrocarbons would be synthesised from the readily available material **165** (Scheme 62) and **167** (Scheme 64) by the reaction sequence described above.

Scheme 68. Proposed syntheses of triamantane (**4**) and tetramantanes (**5** or **6** or **7**)
via rearrangement precursors **171** and **172**.



As in our original plan, the hydrocarbon precursor **88** ($C_{26}H_{32}$) would be anticipated to produce cyclohexamantane (**1**) ($C_{26}H_{30}$) under *dehydrogenative* rearrangement conditions, or the higher diamondoid hydrocarbon pentamantane (**173**)¹² ($C_{26}H_{32}$) under normal rearrangement conditions (Scheme 69).

Scheme 69. Proposed syntheses of cyclohexamantane (**1**) and pentamantane (**173**)
via rearrangement precursor **88**.



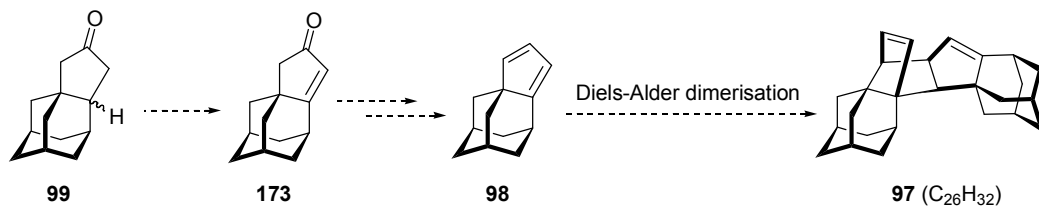
^a Pentamantane has nine isomers. The structure shown here is [1(2,3)4]pentamantane.

We anticipate the completion of this work towards the multi-directional syntheses of hydrocarbon rearrangement precursors, and subsequent acid-catalysed rearrangements to diamondoids within our group will be possible.

2.3. Diels-Alder Dimerisation Approach to Rearrangement Precursor 97

Compared to the four-directional approach to the hydrocarbon rearrangement precursor **88** (Scheme 22), the Diels-Alder dimerisation approach to the hydrocarbon **97** (see section 1.3.3) is more concise (Scheme 70). The monomer **98** would be synthesised from the literature known compound **99**⁴³ through the intermediate adamantanocyclopentenone **173**. Then, [4 + 2] Diels-Alder dimerisation of monomer **98** is expected to furnish the rearrangement precursor **97**.

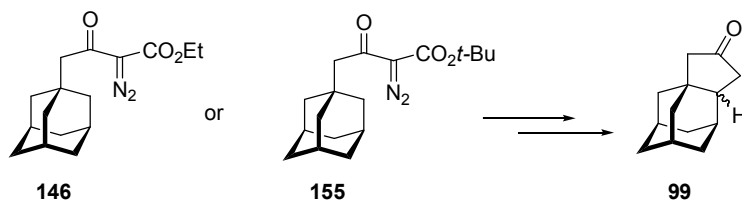
Scheme 70. Proposed synthesis of adamantanocyclopentadiene **98** and subsequent Diels-Alder dimerisation to the dimer **97**.



2.3.1. Synthesis of Adamantanocyclopentanone 99

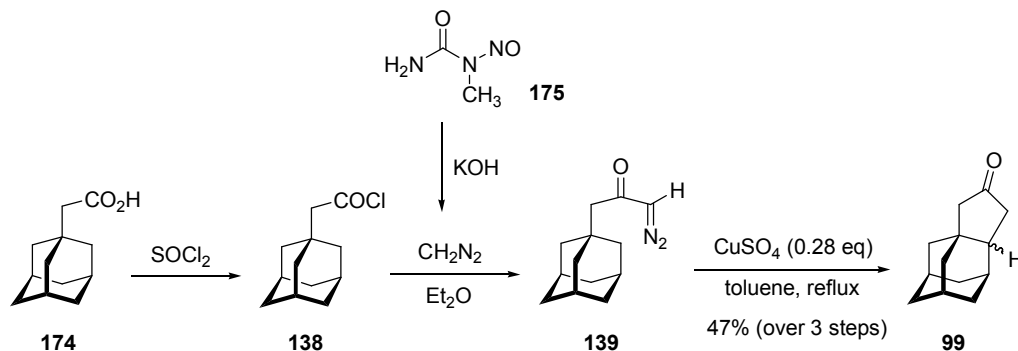
The adamantanocyclopentanone **99** has already been synthesised from two different precursors **146** and **155** in our previous model studies (Scheme 71).

Scheme 71. Synthesis of cyclopentanone **99** from diazo compounds **146** or **155**.



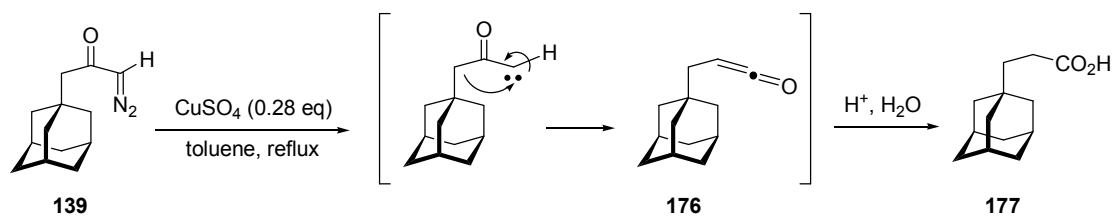
However, we decided to utilise a shorter synthetic approach to adamantanocyclopentanone **99** starting from 1-adamantaneacetic acid chloride (**138**), a known procedure from the literature⁴³ (Scheme 72). Thus, the acid chloride **138** was prepared from the commercially available 1-adamantaneacetic acid (**174**) and thionyl chloride. The α -diazo ketone **139** was then synthesised by reacting the acid chloride **138** with diazomethane, which was generated *in situ* from *N*-nitroso-*N*-methyl urea (**175**) and aqueous KOH solution. Thermal decomposition of a dilute solution diazo compound **139** in the presence of CuSO₄ furnished the desired cyclised product **99** in 47% yield over three steps from carboxylic acid **174**.

Scheme 72. Synthesis of adamantanocyclopentanone **99** from carboxylic acid **174**.



It is worth mentioning that a polar by-product was also isolated (*ca.* 10% yield) from the carbene insertion of diazo compound **139**. This by-product was determined to be 1-admantanepropionic acid (**177**), arising from the undesired Wolff rearrangement pathway through the intermediate ketene **176** described in Scheme 73.

Scheme 73. The by-product **177** from carbene insertion of diazo compound **139**.

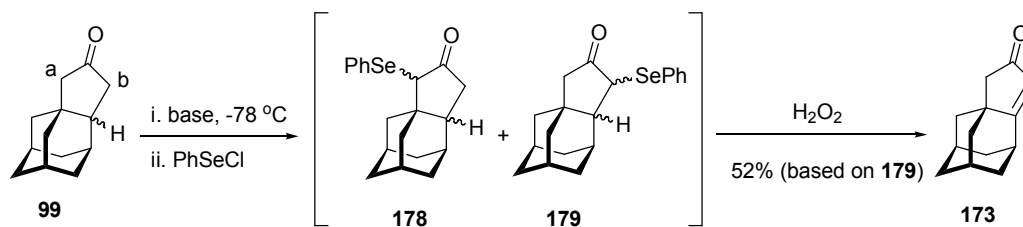


2.3.2. Synthesis of Adamantanocyclopentenone **173**

2.3.2.1. Synthesis of enone **173** Using Selenium Chemistry

We first planned to introduce the carbon-carbon double bond into cyclopentanone **99** by using the reaction sequence of regioselective α -selenylation followed by oxidation and *syn*-elimination. We anticipated that the deprotonation of cyclopentanone **99** would occur favourably on carbon-b, because it is less sterically hindered than carbon-a being next to a quaternary centre (Scheme 74). Thus, the kinetic deprotonation of ketone **99** using LDA followed by reaction with PhSeCl gave an inseparable mixture of two regioisomers **178** and **179** in 47% yield after flash chromatography. However, ^1H NMR analysis revealed the ratio of two regioisomers is 2:1 in favour of the undesired isomer **178**. A better reaction yield was achieved by applying the hindered base LHMDS, which surprisingly gave a lower regioselectivity with the ratio of 10:1 in favour of the undesired isomer **178**. Obviously, among the two regioisomers generated, only selenylated compound **179** would lead to the desired product **173** upon treatment with H_2O_2 followed by *syn*-elimination. Thus, treatment of the mixture of isomers **178** and **179** with H_2O_2 gave the desired cyclopentenone **173** in 52% yield based on compound **179**.

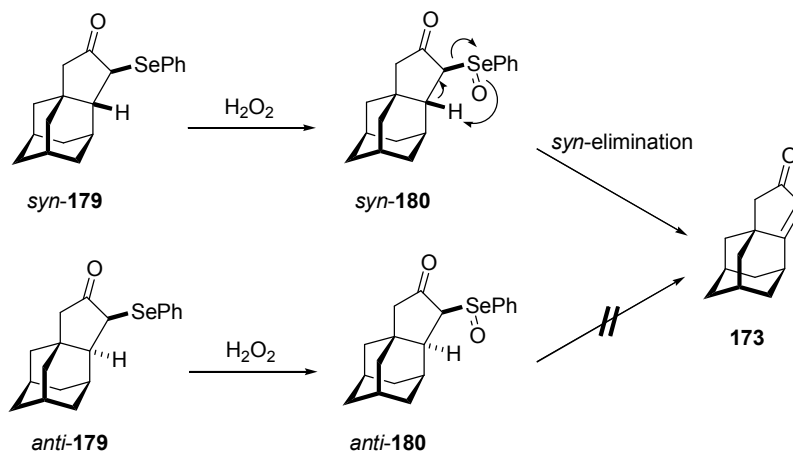
Scheme 74. Synthesis of enone **173** through selenylated compound **179**.



Base	Yield of 1st Step	Ratio of 178/179
LDA	47%	2 : 1
LHMDS	75%	> 10 : 1

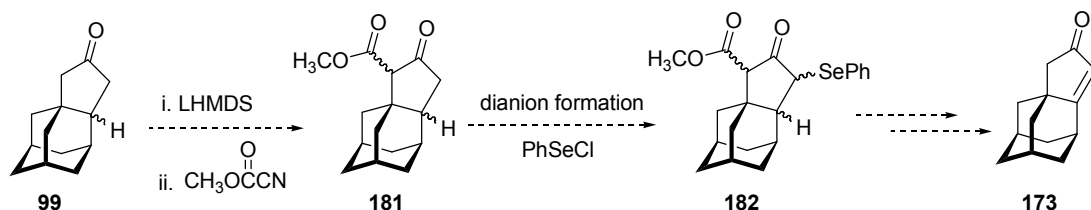
The low yield of the elimination step (**179** → **173**) could be explained in the following scheme. The desired selenylated compound **179** has two diastereomers (*syn*-**179** and *anti*-**179**), however after their oxidation to the selenium oxide **180**, only isomer *syn*-**180** can undergo *syn*-elimination to generate the enone **173** (Scheme 75).

Scheme 75. Mechanism of formation of enone **173** from selenylated compound **179**.



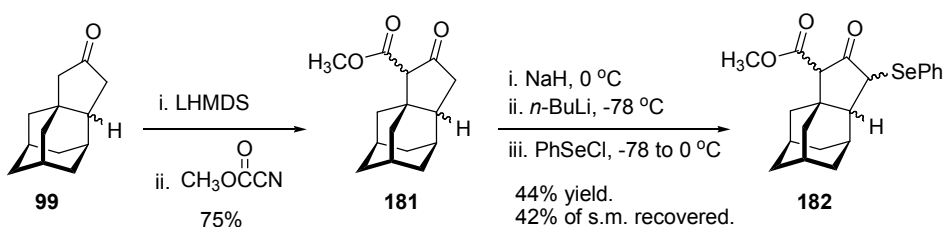
The above synthetic route provided the desired dehydrogenative product **173**, but in low overall yield, owing to the undesired regioselectivity and the low stereoselectivity in the selenylation. This prompted us to search for an alternative approach. Based on the fact that deprotonation of cyclopentanone **99** using LHMDS gave a good regioselectivity (>10:1) in favour of carbon-a (Scheme 74), we anticipated that the β -keto ester **181** would be prepared from ketone **99** in good yield (Scheme 76). Then, dianion formation of β -keto ester **181** followed by quenching with PhSeCl should yield compound **182**, which would be converted to the desired product **173**.

Scheme 76. Proposed synthesis of enone **173** through β -keto ester **181**.



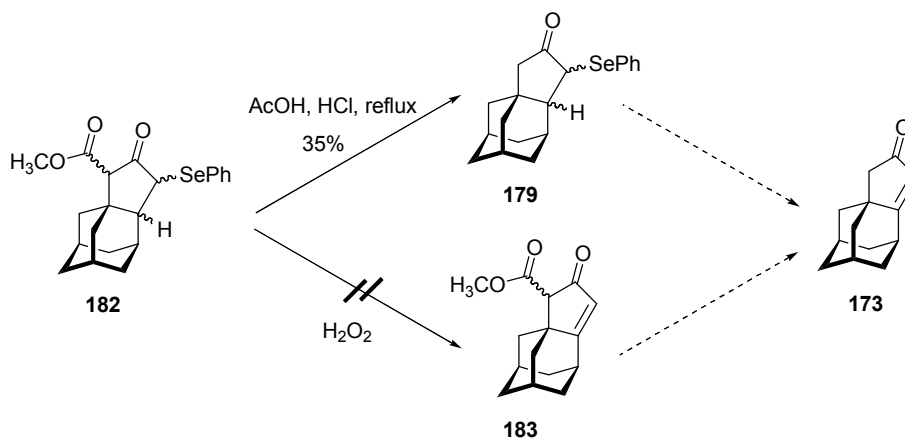
To this end, cyclopentanone **99** was allowed to react with LHMDS, and the corresponding enolate was quenched with Mander's reagent (methyl cyanoformate) (Scheme 77). This step furnished the desired β -keto ester **181** in 75% yield as a 1:1 mixture of two diastereomers. The regioselectivity of this step was greater than 10:1 by the ^1H NMR analysis of the crude product. Unfortunately, dianion generation by treatment of β -keto ester **181** with NaH and *n*-BuLi sequentially, followed by reaction with PhSeCl, led to the desired product **182** in only moderate yield (44%) along with 42% of starting material recovered.

Scheme 77. Synthesis of selenylated compound **182** from adamantanocyclopentanone **99**.



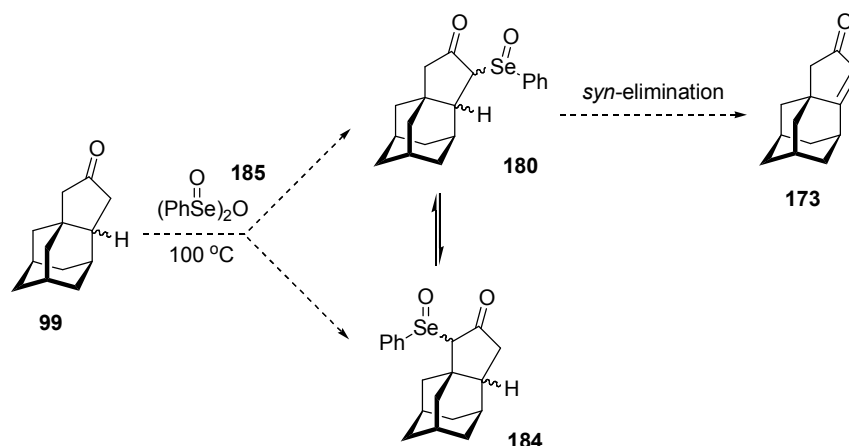
Nevertheless, with the selenylated β -keto ester **182** in hand, a two-step reaction sequence (dealkoxycarbonylation of methyl ester and subsequent oxidative elimination of selenium substituent) was then attempted to yield cyclopentenone **173**. Disappointingly, dealkoxycarbonylation of β -keto ester **182** under acidic refluxing conditions generated the desired product **179** in only 35% yield (Scheme 78). In addition, Krapcho dealkoxycarbonylation of β -keto ester **182** using KCN and H_2O in DMSO failed to furnish any desired product **179**. As an alternative approach, oxidative elimination of selenylated compound **182** with H_2O_2 first to enone **183** was also carried out, unfortunately no reaction was observed.

Scheme 78. Attempted synthesis of enone **173** from selenylated compound **182**.



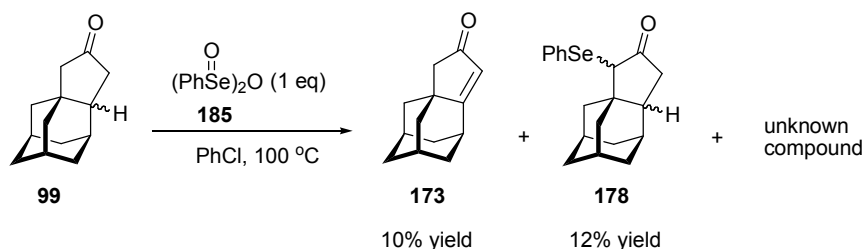
In an effort to search for other possible synthetic transformations from ketone **99** to enone **173**, we found that Ley and co-workers reported a one-pot procedure for the dehydrogenation of steroidal and triterpenoid ketones using benzeneseleninic anhydride.⁶⁹ Based on this literature precedent, we speculated that the cyclopentanone **99**, *via* its enol form, would react with benzeneseleninic anhydride (**185**) to give two isomers **180** and **184** as intermediates (Scheme 79). It was expected that at 100 °C, the two intermediates **180** and **184** would be in equilibrium in favour of the compound **180**, which could then undergo *syn*-elimination to furnish the product **173**, thus solving the regioselectivity problem.

Scheme 79. Proposed synthesis of enone **173** from cyclopentanone **99** using benzeneseleninic anhydride (**185**).



Therefore, cyclopentanone **99** was reacted with benzeneseleninic anhydride (**185**) at 100 °C in chlorobenzene (Scheme 80). Unfortunately, this reaction provided the desired product **173** in poor yield, along with the undesired selenylated compound **178** isolated in 12% yield and another unknown compound.

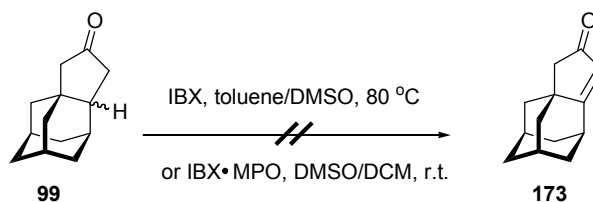
Scheme 80. Attempted synthesis of enone **173** from cyclopentanone **99** with benzeneseleninic anhydride (**185**).



2.3.2.2. Attempted Synthesis of Enone **173** by IBX Oxidation

Since the dehydrogenation of cyclopentanone **99** using selenium chemistry had failed to provide the desired product **173** in an acceptable yield, we next turned our attention to the direct synthetic transformation of cyclopentanone to cyclopentenone. Recently, Nicolaou and co-workers reported an efficient dehydrogenation of ketones to α,β -unsaturated carbonyl motif mediated by the iodine(V) species IBX (*o*-iodoxybenzoic acid).⁷⁰ The complex IBX · MPO (4-methoxypyridine-*N*-oxide) was also developed as an effective dehydrogenation reagent for carbonyl compounds under remarkably mild conditions.⁷⁰ Therefore, we attempted this reaction on our substrate **99** using both IBX at elevated temperature and IBX · MPO complex at ambient temperature (Scheme 81). Unfortunately, under both conditions, there was no conversion to the product **173** with only starting material **99** recovered.

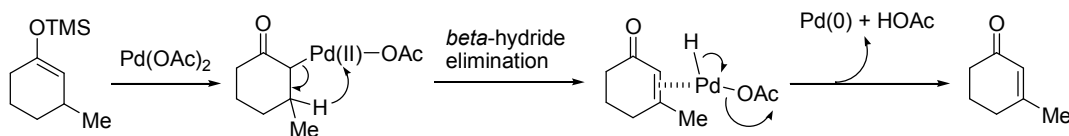
Scheme 81. Attempted synthesis of enone **173** by IBX oxidation of ketone **99**.



2.3.2.3. Synthesis of Enone **173** by Saegusa Oxidation

The Saegusa oxidation is a standard method for the conversion of a silyl enol ether into the corresponding α,β -enone. We were interested in this transformation because it is a one-pot two-step procedure, thus allowing us to have a quick access to enone **173**. The postulated mechanism of the Saegusa oxidation is described in Scheme 82.⁷¹ The oxidant $\text{Pd}(\text{OAc})_2$ can be used in either stoichiometric amounts, or catalytic amounts in the presence of a co-oxidant.

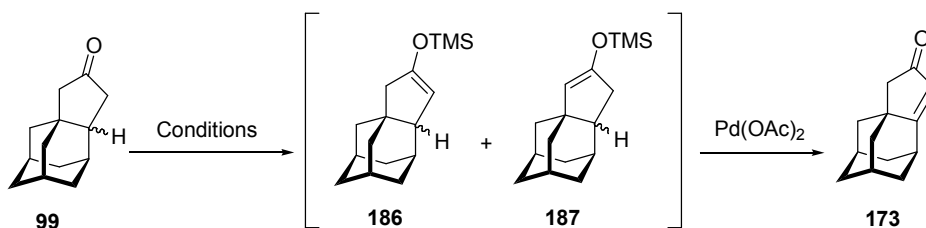
Scheme 82. Postulated mechanism of the Saegusa oxidation.



In our case, when cyclopentanone **99** is treated with base followed by treatment with TMSCl , two silyl enol ethers **186** and **187** will be formed (Table 9). After the Saegusa oxidation of the crude mixture, whilst the desired isomer **186** will lead to the product **173**, the undesired isomer **187** will give back starting material **99** after work-up. Therefore, when LDA was used as a base, the reaction generated the desired product **173** in 16% over two steps with 35% of starting material **99** recovered (Entry 1, Table 9). The use of LTMP (lithium 2,2,6,6-tetramethyl piperidine) gave a better overall yield (Entry 2, Table 9). From an economic point of view, it would be nice to utilise catalytic quantities of $\text{Pd}(\text{OAc})_2$

rather than stoichiometric amounts. Larock has reported the catalytic version of the Saegusa oxidation by regeneration of the Pd(II) oxidant using oxygen at elevated temperatures.⁷² However, this catalytic reaction gave a lower yield of the product **173** in our hands (Entry 3, Table 9).

Table 9. Synthesis of enone **173** by the Saegusa oxidation of silyl enol ether **186**.



Entry	Conditions	Results
1	LDA, TMSCl; $\text{Pd}(\text{OAc})_2$ (1.1 eq)	16% yield of 173 + 35% of 99 recovered.
2	LTMP, TMSCl; $\text{Pd}(\text{OAc})_2$ (1 eq)	23% yield of 173 + 33% of 99 recovered.
3	LTMP, TMSCl; $\text{Pd}(\text{OAc})_2$ (0.1 eq), O_2 , DMSO, 60 °C	17% yield of 173 + 37% of 99 recovered.
4	$\text{Me}_3\text{SiCH}_2\text{CO}_2\text{Et}$, TBAF(0.03 eq); $\text{Pd}(\text{OAc})_2$ (1 eq), benzoquinone	17% yield of 173 + 25% of 99 recovered.
5	$\text{Me}_3\text{SiCH}_2\text{CO}_2\text{Et}$, TBAF(0.03 eq); $\text{Pd}(\text{OAc})_2$ (1 eq)	9% yield of 173 + 38% of 99 recovered.

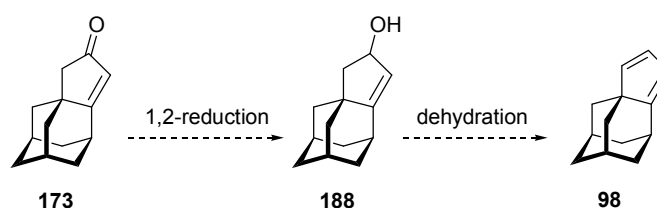
We also found a paper by Crimmins and co-workers⁷³ that, in a very similar cyclopentanone system, surprisingly high regioselectivity in the formation of silyl enol ethers was achieved by using ethyl (trimethylsilyl)acetate and catalytic amounts of tetrabutylammonium fluoride⁷⁴ rather than any dialkylamide bases. Unfortunately, these reaction conditions failed to furnish the desired product **173** in a better yield (Entries 4 and 5, Table 9).

2.3.3. Synthesis of Adamantanocyclopentadiene **98**

2.3.3.1. Synthesis of Diene **98** from Enone **173**

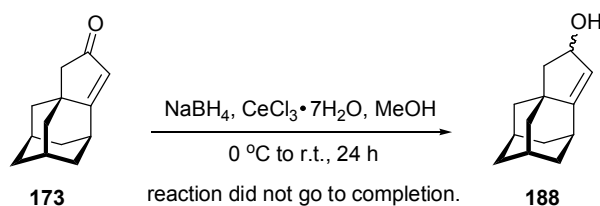
With the enone **173** in hand, we next wished to carry out its 1,2-reduction to give allylic alcohol **188** and the subsequent dehydration to furnish diene **98** (Scheme 83).

Scheme 83. Proposed synthesis of diene **98** from enone **173**.



Thus, 1,2-reduction of adamantanocyclopentenone **173** using Luche reaction conditions (NaBH_4 , $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$) gave an inseparable mixture of the desired allylic alcohol **188** and starting material **173** (Scheme 84).

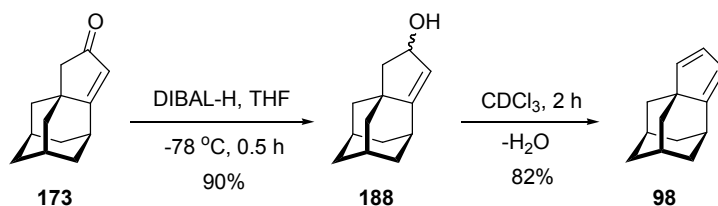
Scheme 84. Luche reduction of enone **173** to allylic alcohol **188**.



Pleasingly, DIBAL-H reduction of the cyclopentenone **173** at low temperature ($-78\text{ }^\circ\text{C}$) furnished the desired 1,2-reduced product **188** in excellent yield (Scheme 85). Interestingly, the ^1H NMR of allylic alcohol **188** in deuterated chloroform indicated the presence of a mixture of allylic alcohol **188** and the dehydrated compound **98**. (Scheme 83). Two hours after the dissolution in CDCl_3 , the compound **188** was transformed to the dehydrated product **98** in quantitative yield. The purification of diene **98** by flash chromatography

provided the pure product in 82% yield, which was due to the volatile property of the material and its loss during the drying procedure.

Scheme 85. DIBAL-H reduction of enone **173** and the subsequent dehydration to diene **98**.

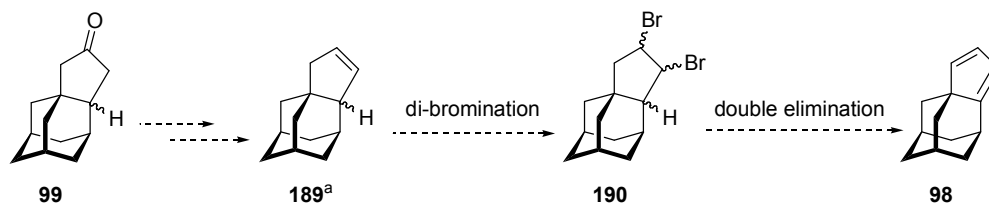


As for the cause of the formation of diene **98** in CDCl₃, we reasoned that the trace amounts of acid present in the deuterated chloroform catalysed the dehydration process. Indeed, when the allylic alcohol **188** was characterised in deuterated benzene in which no trace amounts of acid are present, no dehydration product **98** was observed.

2.3.3.2. Other Attempted Synthesis of Diene **98**

Although the synthesis of diene **98** was achieved from adamantanocyclopentenone **173**, the synthesis of enone **173** was not satisfactory due to the low overall yield from ketone **99** as described in section 2.3.2. Therefore, as an alternative approach to diene **98**, we envisaged that ketone **99** could be converted to the olefin **189**, which would then undergo dibromination and the subsequent double elimination to yield the diene **98** (Scheme 86).

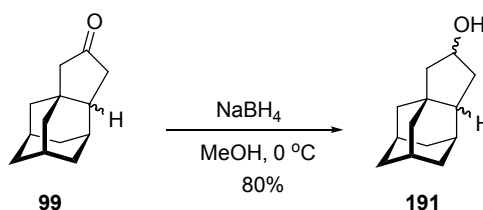
Scheme 86. Proposed synthesis of diene **98** from olefin **189**.



^a The structure shown here is a representative of two possible regioisomer.

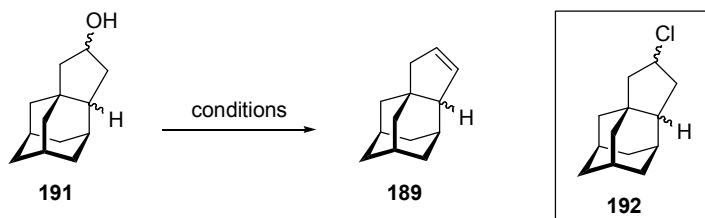
Accordingly, NaBH₄ reduction of ketone **99** smoothly furnished the corresponding alcohol **191** in good yield (Scheme 87).

Scheme 87. Reduction of ketone **99** to alcohol **191**.



With alcohol **191** in hand, we next studied its dehydration to olefin **189** (Table 10). When cyclopentanol **191** was treated with POCl₃ and pyridine, no desired dehydration product **189** was obtained. Instead, the displacement product **192** was isolated in 74% yield (Entry 1, Table 10). The use of Martin's sulfurane dehydrating reagent (**193**) only resulted in the isolation of trace amounts of desired product **189** by ¹H NMR analysis along with some unknown products (Entry 2, Table 10).⁷⁵ Unfortunately, the efficient Burgess dehydrating reagent (**194**) failed to produce any desired product **189** (Entry 3, Table 10).⁷⁵

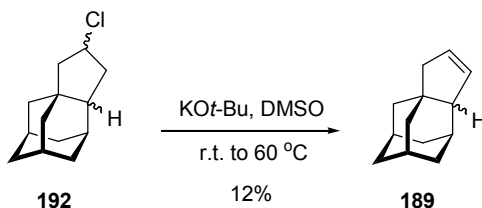
Table 10. Attempted synthesis of olefin **189** from alcohol **191**.



Entry	Conditions	Results
1	POCl ₃ , pyridine	74% of displacement product 192 isolated.
2	Ph ₂ S[OC(CF ₃) ₂ Ph] ₂ (193), CH ₂ Cl ₂	trace amount of 189 and unknown compounds.
3	Et ₃ N ⁺ -S(=O) ₂ ⁻ -N-CO ₂ CH ₃ (194), CH ₃ CN, reflux	complex mixture of unknown compounds.

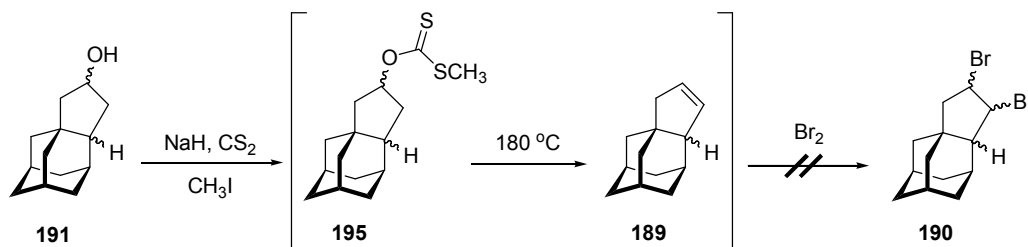
Since we obtained chloride **192** as a by-product from the attempted dehydration of alcohol **191**, its elimination of HCl to olefin **189** using potassium *tert*-butoxide was attempted (Scheme 88). However, this reaction only gave the desired product **189** in very low yield.

Scheme 88. Elimination of chloride **192** to olefin **189**.



We also attempted the Chugaev elimination of xanthate **195** generated *in situ* from alcohol **191** to give olefin **189** as a crude product, which was then taken to the next di-bromination step (Scheme 89). Disappointingly, this approach failed to furnish any desired product **190**.

Scheme 89. Attempted synthesis of di-bromide **190**.

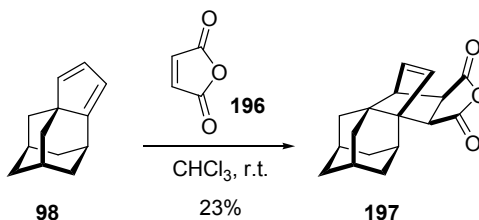


Due to time constraints, it was not possible to further pursue this synthetic approach to diene **98** *via* olefin **189**. Considering that these preliminary results were discouraging, we decided to abandon this synthetic route and to prepare diene **98** *via* enone **173** as described in section 2.3.3.1.

2.3.4. Attempted Diels-Alder Dimerisation of Diene **98** and Structural Elucidation

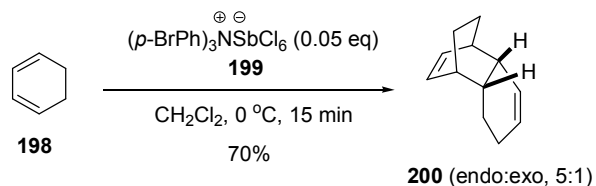
With the key diene **98** in hand, we were in a position to investigate the crucial Diels-Alder dimerisation to furnish the rearrangement precursor **97** (Scheme 70). We began the investigation with a test Diels-Alder reaction of the diene **98** and a reactive dienophile maleic anhydride (**196**) (Scheme 90). Although this test reaction generated the desired adduct **197** in low yield, it demonstrated the good reactivity of compound **98** as a diene partner in the Diels-Alder reaction.

Scheme 90. Diels-Alder reaction of diene **98** and dienophile **196**.



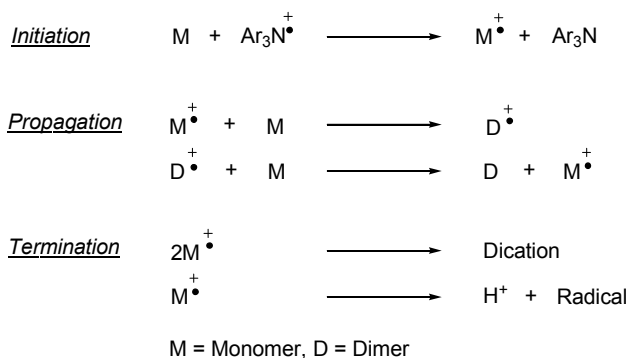
The especially high reactivity of electron-deficient dienophiles in the Diels-Alder reaction is a common characteristic of this strategic synthetic reaction.⁷⁶ Clearly, our diene **98** is not a reactive dienophile partner in the Diels-Alder reaction, as it is an electron-rich olefin. However, we were encouraged by the examples of aminium cation-radical enhanced reactivity of electron rich dienophiles in the literature.^{76,77} One of these examples is shown in Scheme 91. The uncatalysed Diels-Alder dimerisation of 1,3-cyclohexadiene (**198**) has been effected in 30% yield after 20 h at 200 °C.⁷⁸ However, when diene **198** was exposed to catalytic quantities of the stable cation-radical salt tris(*p*-bromophenyl)aminium hexachloroantimonate (**199**) in CH_2Cl_2 at 0 °C, the Diels-Alder dimerisation product **200** was obtained in 70% yield within 15 min.

Scheme 91. Aminium cation-radical catalysed Diels-Alder dimerisation of diene **198**.



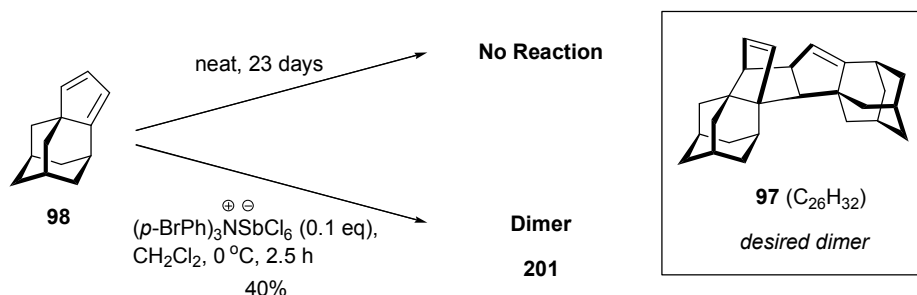
The cation-radical chain mechanism is described in Scheme 92. The reactivity constraints of electron-rich dienophiles is relieved by conversion of these species to their corresponding cation radicals, which react readily with appropriate dienes since they are rather highly electron-deficient. The neutral or electron-rich substrates suitable for this method must be readily ionised to cation radicals,⁷⁶ and our diene **98** fall into this category.

Scheme 92. The cation-radical chain mechanism.



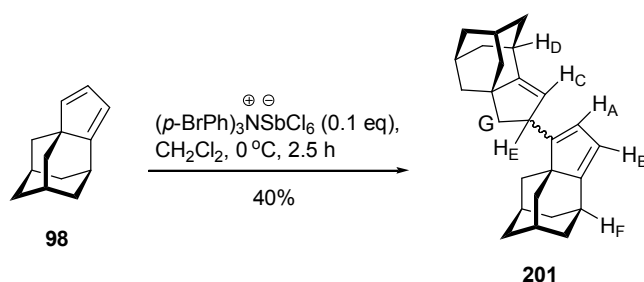
Indeed, when neat diene **98** was left at room temperature for prolonged periods (23 days), no reaction took place in the flask with only starting material recovered (Scheme 93). However, when diene **98** was treated with catalytic amounts of the cation-radical salt tris(*p*-bromophenyl)aminium hexachloroantimonate (**199**) in CH_2Cl_2 at $0\text{ }^\circ\text{C}$, the dimer **201** was obtained in 40% yield. By MS and HRMS analysis, we were confident that the dimer of diene **98** was formed. In addition, ^1H NMR showed three vinyl protons, which should be present in the desired dimerised product **97**.

Scheme 93. Attempted Diels-Alder dimerisation of diene **98** to dimer **97**.



However, the ^{13}C NMR of dimer **201** clearly showed that there are six olefinic carbons present, instead of four in the desired dimer **97**. This fact led us to examine the structure of dimer **201** more carefully. Therefore, we carried out extensive studies on the spectroscopic data of dimer **201**, including ^1H / ^{13}C NMR, ^1H COSY, ^{13}C DEPT, $^1\text{H}/^{13}\text{C}$ correlation and UV-vis. As a result of this, we ruled out other possible structures and proposed that the structure of the dimer is not the desired [4 + 2] dimer **97**, but a dimer with only one carbon-carbon single bond linking the two monomer units **98** as shown in Scheme 94.

Scheme 94. Cation-radical catalysed Diels-Alder dimerisation of diene **98** to dimer **201**.

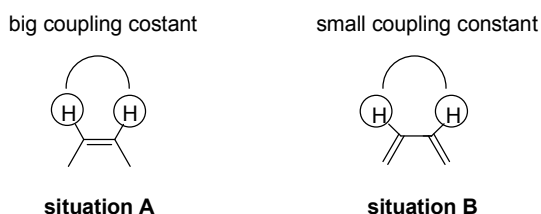


Clearly a product this unexpected requires some further discussion with regard to its assignment. The proposed structure **201** was elucidated based on the following key facts and explanations.

- The product **201** has the molecular formula of $\text{C}_{26}\text{H}_{32}$ as confirmed by MS and high resolution MS.

- There are three vinyl protons (6.30, 5.93, 5.21 ppm) in the structure **201** as can be seen from ^1H NMR (Figure 8).
- There are three quaternary olefinic carbons (162.2, 157.9 and 153.0 ppm) and three tertiary olefinic carbons (123.9, 117.4, 114.6 ppm), as can be seen from ^{13}C NMR (Figure 9) and ^{13}C DEPT (Figure 10).
- From ^1H NMR and ^1H COSY, the two adjacent vinyl protons (6.30 and 5.93 ppm), which are correlated to each other have the coupling constant of 1.9 Hz. This small coupling constant indicates that the two vinyl protons must not reside on the same carbon-carbon double bond (**situation A**, Scheme 95), but must reside on two *different* carbon-carbon double bonds (**situation B**, Scheme 95). H_A (6.30 ppm) and H_B (5.93 ppm) in the structure **201** shown in Scheme 94 represent these two vinyl protons.

Scheme 95. Coupling constant of two vinyl protons.



- There are three relative low-field proton signals with the chemical shifts of 3.74 ppm, 2.98 ppm and 2.75 ppm, respectively. These three protons must be positioned next to a carbon-carbon double bond (H_D , H_E and H_F in the structure **201** in Scheme 94).
- Considering ^1H COSY and $^1\text{H}/^{13}\text{C}$ correlation, one proton (3.72 ppm) next to a carbon-carbon double bond has the correlation with one vinyl proton and two protons in a CH_2 unit (H_E in the structure **201** in Scheme 94).
- Considering UV-vis spectrum, the absorption peak is at 262 nm indicating it is very unlikely that the third carbon-carbon double bond is in conjugation with the cyclopentadiene unit. If the third double bond was conjugated with the cyclopentadiene unit, the absorption maximum would shift towards longer

wavelengths according to the Woodward-Fieser rules.⁷⁹ The rules tell us the absorption maximum for the parent cyclopentadiene is at 244 nm and further π conjugation will add 30 nm to the parent value. In addition, the alkyl substituents on the cyclopentadiene ring will also add some value to the parent value.

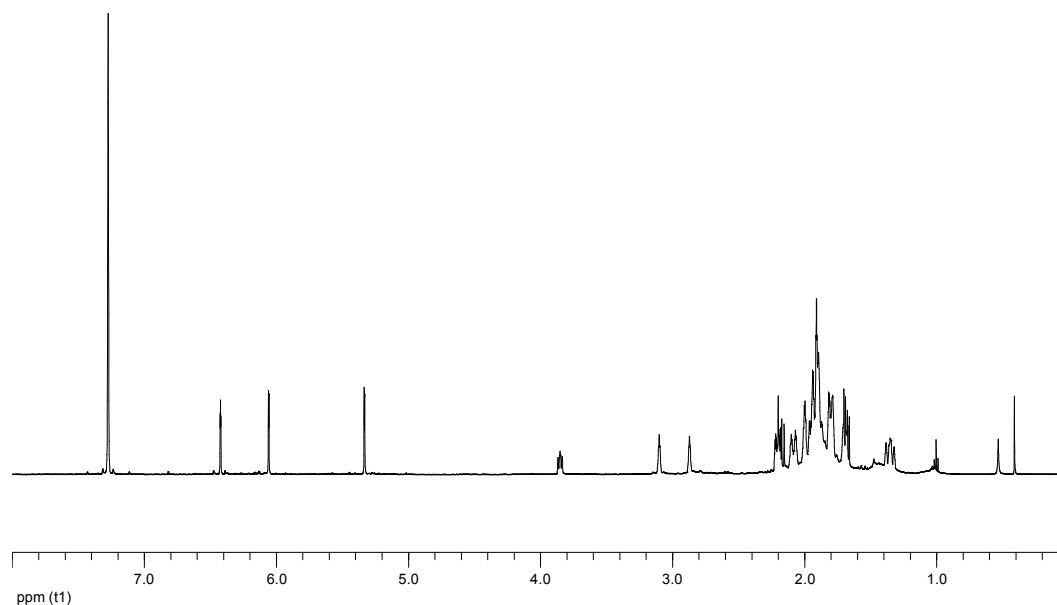


Figure 8. ¹H NMR of dimer **201** in C₆D₆ (500 MHz).

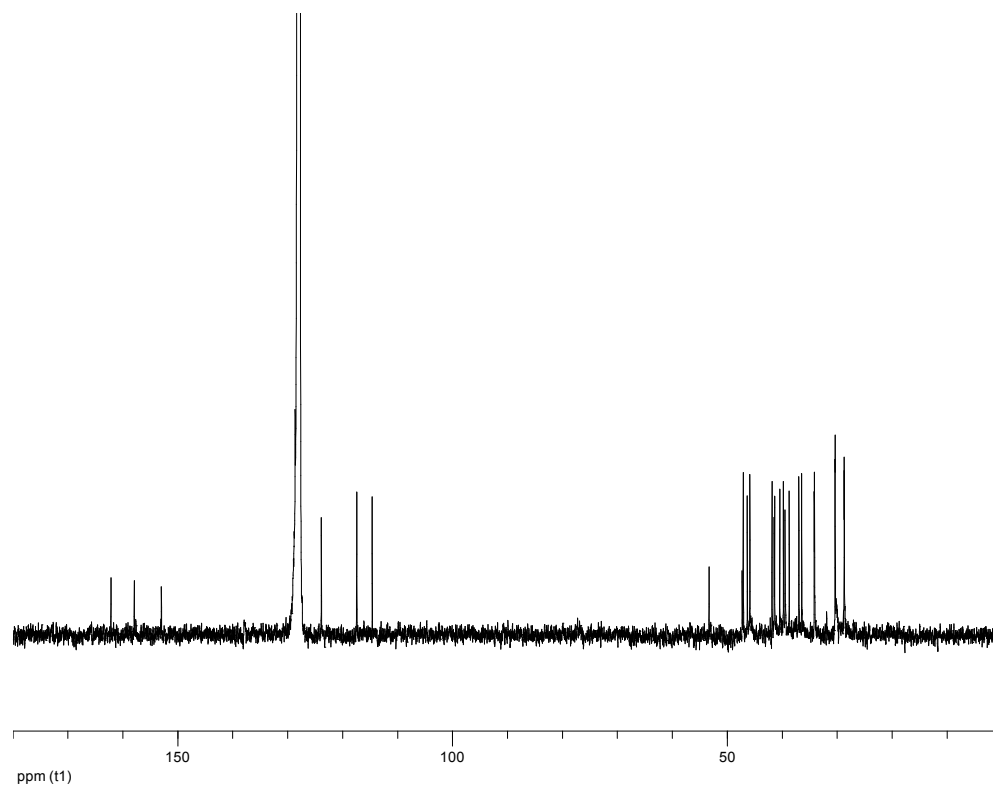


Figure 9. ^{13}C NMR of dimer **201** in C_6D_6 (100 MHz).

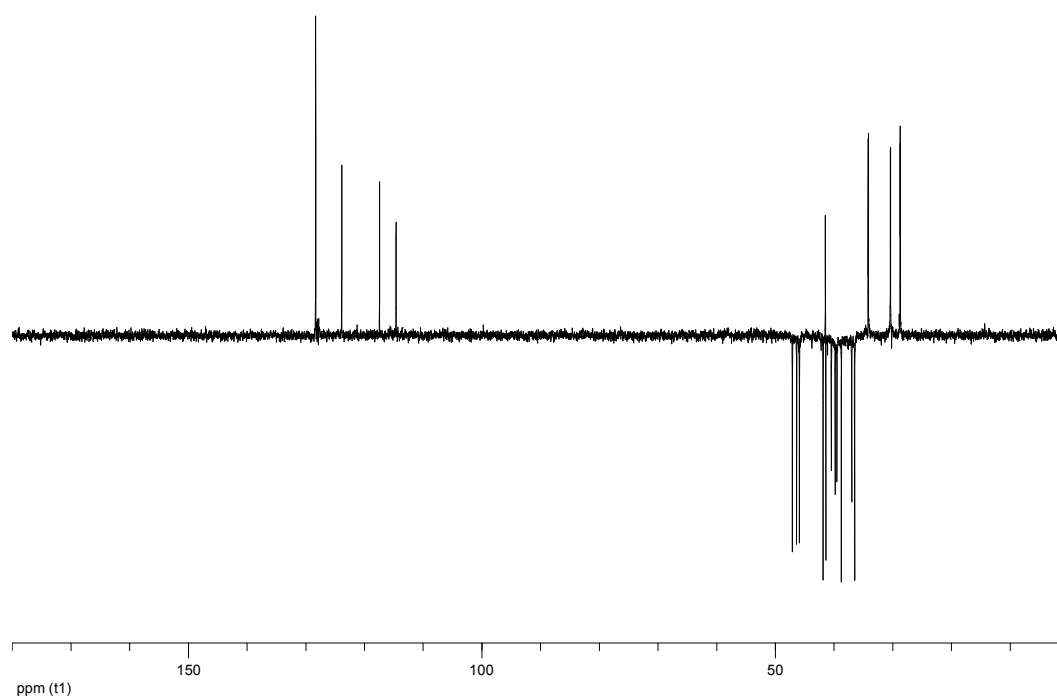


Figure 10. ^{13}C DEPT of dimer **201** in C_6D_6 (125 MHz).

Another interesting aspect of dimer **201** (Scheme 94) is that it undergoes partial decomposition in CDCl_3 , and the original colourless solution turns green. This indicates to us the instability of triene **201** towards trace amounts of acid which are present in CDCl_3 . Therefore, the NMR of dimer **201** was taken in deuterated benzene. Although an X-ray crystal structure of dimer **201** is highly desirable to fully confirm our proposed structure, we were unable to obtain crystals due to the oily property of the dimer **201**.

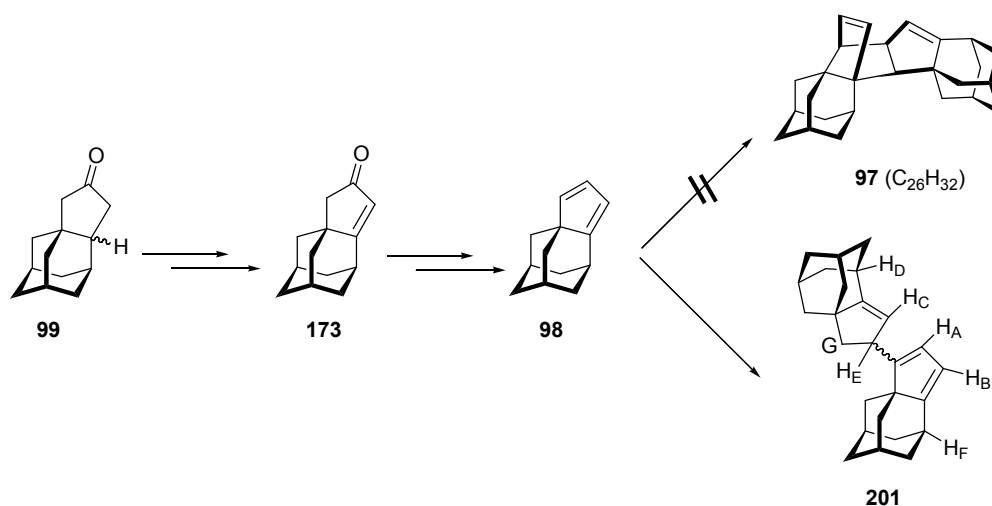
Of course, the formation of this unexpected dimer **201** is of great interest with regard to the mechanism. However, due to time constraints, it was not possible for us to carry out further mechanistic study of this reaction.

Whilst dimer **201** can be synthesised from monomer **98** in moderate yield, the proposed structure (Scheme 94) is not suitable to serve as a rearrangement precursor as planned in our synthetic approach (Scheme 70). With only one carbon-carbon single bond linkage, dimer **201** is expected to undergo decomposition rather than rearrangement when treated with Lewis acids or superacids. Unfortunately, due to time constraints and lack of material, we were unable to attempt the acid catalysed rearrangement of dimer **201**.

2.3.5. Conclusions and Future Work

Despite the considerable difficulties encountered in the synthesis of enone **173**, we were able to prepare diene **98** in synthetically useful amounts from the literature known compound **99**⁴³ (Scheme 96). Additionally, our limited investigation into the aminium cation-radical catalysed Diels-Alder dimerisation of monomer **98** failed to furnish the desired rearrangement precursor **97** and generated the dimer **201** instead. Extensive efforts have been made towards elucidating the structure of dimer **201** by the analysis of its spectroscopic data.

Scheme 96. Attempted synthesis of dimer **97** from cyclopentanone **99**.



Owing to time constraints it was not possible to investigate this strategy further. A more detailed investigation into the cation-radical catalysed Diels-Alder reaction conditions would be required to advance this study. Additionally, other methods of Diels-Alder dimerisation need to be studied to furnish the desired dimer **97**. It is hoped that the use of protic acid catalysed or high pressure Diels-Alder dimerisation⁸⁰ would possibly yield the desired [4 + 2] dimer **97**. We anticipate that completion of this work towards the synthesis of dimer **97** and subsequent dehydrogenative rearrangement to cyclohexamanatane (**1**) will be possible in the future work within our group.

3. EXPERIMENTAL

General Experimental Techniques

Instrumental

Melting points were obtained on a Reichert-Thermovar melting point apparatus and are uncorrected. Infrared spectra were recorded on Unicam and Mattson FTIR spectrometers with automatic background subtraction. Samples were prepared as thin films on sodium chloride plates with absorptions reported in wavenumbers (cm^{-1}). Proton magnetic resonance spectra (^1H NMR) were recorded at 300 MHz, 400 MHz and 500 MHz on Bruker DRX-300, Bruker DRX-400 and Bruker AM-500 spectrometers respectively. UV-vis spectra were recorded using a Spectronic Unicam UV 500 series UV-vis spectrometer. Chemical shifts (δ) are quoted in parts per million (ppm) and are referenced to the residual solvent peak, 7.27 for CDCl_3 , 7.15 for C_6D_6 , 3.34 for methanol- d_4 , 2.52 for DMSO- d_6 . Carbon magnetic resonance spectra (^{13}C NMR) were recorded at 75 MHz, 100 MHz and 125 MHz on Bruker DRX-300, Bruker DRX-400 and Bruker AM-500 spectrometers respectively. Chemical shifts (δ) are quoted in parts per million (ppm) and are referenced to the residual solvent peak, 77.0 for CDCl_3 , 128.6 for C_6D_6 , 49.9 for methanol- d_4 , 39.7 for DMSO- d_6 . Coupling constants (J) are quoted in Hertz (Hz) for ^1H and ^{13}C NMR. Spectra recorded on the Bruker DRX-400 and Bruker AM-500 spectrometers were carried out by the Imperial College Department of Chemistry NMR service. Mass spectrometry (EI, CI, ES, FAB) was recorded by the Imperial College Department of Chemistry Mass Spectrometry Service using a Micromass Platform II spectrometer (low resolution) and a Micromass Autospec Q spectrometer (low and high resolution). Elemental analyses were determined by the Department of Health and Human Sciences at London Metropolitan University. UV detection was performed using a Waters 600 Diode Array detector, and all analyses were performed using MassLynx 3.1. Optical rotations were recorded at 22 °C on a Perkin-Elmer 241 polarimeter with a path length of 1 dm, using the 589.3 nm D-line of sodium. Concentrations (c) are quoted in g / 100 mL.

Experimental procedures

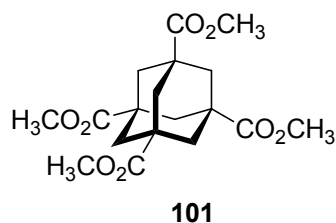
All reactions were carried out in oven or flame-dried glassware under an inert atmosphere of nitrogen or argon. Reaction temperatures other than room temperature were recorded as bath temperatures unless otherwise stated.

Solvents were purchased from BDH laboratory supplies, or the Aldrich Chemical Company. Solvents for flash chromatography were reagent or GPR grade and were used as received. Reaction solvents were distilled as specified. CH₂Cl₂, MeOH, pyridine and Et₃N were distilled from calcium hydride under a nitrogen atmosphere. Diethyl ether and THF were distilled from sodium benzophenone ketyl under a nitrogen atmosphere. Toluene was distilled from sodium under a nitrogen atmosphere.

Column chromatography was performed on Merck silica gel 60, particle size 20-63 µm or BDH silica gel, particle size 33-70 µm. Analytical thin layer chromatography (TLC) was performed on Merck silica gel 60 F₂₅₄ glass-backed plates. Visualisation was accomplished by ultraviolet light 254 nm and/or chemical staining using potassium permanganate dip and drying with a heat gun. All chromatography eluents were BDH GPR grade and used without purification. Petrol refers to BDH AnalaR GPR petroleum spirit 40-60 °C.

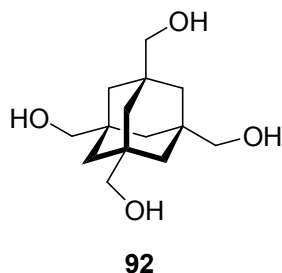
Conventions adopted in Experimental section

All compounds reported herein are either novel or are literature known compounds. In the latter case, these have been referenced and the data obtained is consistent with the literature. Reported compounds are in sequential order as described in the **Results and Discussion** section, to help readers locate each compound. All reported compounds have been reported according to the *J. Org. Chem.* format. In cases where diastereomeric/isomeric compounds were observed, judgement was used to either report signals for the major isomer, the entire mixture of isomers or each isomer separately, depending upon the ease of analysis.

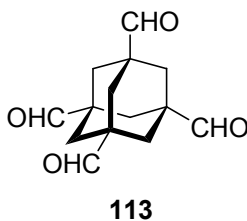


1,3,5,7-Tetracarbomethoxyadamantane 101.⁴⁸ To 1,3-adamantanedicarboxylic acid **29** (10.0 g, 44.6 mmol) in a flask fitted with a reflux condenser was added freshly distilled thionyl chloride (60 mL). The mixture was refluxed with vigorous stirring for 2 h and the excess thionyl chloride was removed *in vacuo*. The mixture was cooled to room temperature and dry benzene (50 mL) was added which was further removed *in vacuo* to give an off-white precipitate. The solid was placed under vacuum for 12 h to afford 11.7 g (quantitative yield) of crude 1,3-adamantanedicarbonyl chloride **112** as an off-white solid. Spectroscopic data were consistent with the reported values.⁵²

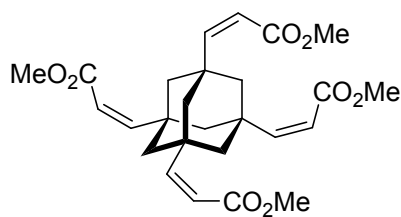
A clear solution of 1,3-adamantanedicarbonyl chloride **112** (11.7 g, 44.6 mmol) in oxalyl chloride (130 mL) was irradiated at 20 °C by a medium pressure, quartz, mercury-vapor lamp (450 Watts) immersed into a double-walled quartz well with inlet and outlet tubes for cooling. The reaction vessel constructed of glass was placed outside the immersion well with one vertical joint for condenser. After 16 h of irradiation, the excess oxalyl chloride was removed on a rotary evaporator and the residue was stirred with dry MeOH (80 mL) at room temperature overnight. The mixture was concentrated *in vacuo*, and the oily residue was dissolved in EtOAc (100 mL), washed with 5% aqueous Na₂CO₃ (30 mL), then brine (30 mL). The organic layer was dried with MgSO₄, filtered, and concentrated *in vacuo*. The desired product was isolated by vacuum filtration after triturating the residue with minimal amount of MeOH to afford 4.2 g (25%, over 2 steps) of tetra-methyl ester **101** as colourless crystals: m.p. 167 - 168 °C (hexanes : EtOAc, 5 : 1) (lit. m.p. 168 - 170 °C); *R_f* 0.36 (hexanes : EtOAc, 2 : 1); IR (film) 2955, 1725, 1429, 1306 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 3.69 (s, 12H, OCH₃), 1.99 (s, 12H, CH₂); ¹³C NMR (75 MHz, CDCl₃) δ 175.5, 52.1, 41.7, 38.5; MS (ES) *m/z* 369 (M+H⁺); HRMS (ES) *m/z* calc for C₁₈H₂₅O₈ 369.1549, found: 369.1559.



1,3,5,7-Tetrakis(hydroxymethyl)adamantane 92.⁴² A solution of tetra-ester **101** (3.0 g, 8.15 mmol) in THF (40 mL) was added dropwise to a suspension of lithium aluminum hydride (1.24 g, 32.6 mmol) in THF (32 mL) at 0 °C under argon. The reaction mixture was then refluxed for 3 h, cooled and a minimal amount of saturated aqueous Na₂SO₄ (2.43 mL) was added carefully to quench the reaction. The reaction mixture was stirred for an additional 30 min, then THF (40 mL), MeOH (40 mL) and silica gel (2.0 g) were added, and the mixture was filtered through a short pad of Celite. Rotary evaporation and flash chromatography (CH₂Cl₂ : MeOH, 10:1 → 8:1) gave tetra-ol **92** as a white solid (1.90 g, 91%): m.p. 226 - 228 °C (MeOH); *R_f* 0.36 (CH₂Cl₂ : MeOH, 4 : 1); IR (film) 3323 broad, 2919, 2851, 1576 cm⁻¹; ¹H NMR (300 MHz, MeOH-*d*₄) δ 3.26 (s, 8H, CH₂OH), 1.21 (s, 12H, CH₂); ¹³C NMR (75 MHz, MeOH-*d*₄) δ 73.3, 41.5, 37.2; MS (EI) *m/z* 256 (M⁺); HRMS (EI) *m/z* calc for C₁₄H₂₄O₄ 256.1675, found: 256.1678.

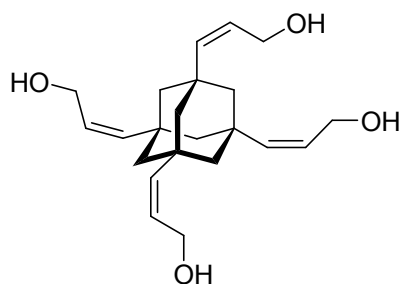


1,3,5,7-Tetraformyladamantane 113.⁵³ A solution of oxalyl chloride (2.82 mL, 32.9 mmol) in CH₂Cl₂ (18 mL) was cooled to -78 °C. Under vigorous stirring, anhydrous DMSO (4.66 mL, 65.7 mmol) in CH₂Cl₂ (12 mL) was added over 10 min, and the reaction mixture was stirred at this temperature for an additional 15 min. A solution of tetra-ol **92** (990 mg, 3.87 mmol) in a mixture of anhydrous DMSO (15 mL) and CH₂Cl₂ (30 mL) was added dropwise over a period of 10 min, and the reaction mixture was stirred at -78 °C for an additional 1 h. After this, triethylamine (22 mL) was added dropwise, and the mixture was allowed to warm up to room temperature. Water (60 mL) was added and the two phases were separated. The organic layer was washed with 5% aqueous HCl (20 mL), water (20 mL), 5% aqueous NaHCO₃ solution (40 mL) and brine (20 mL), dried over MgSO₄, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (hexanes : EtOAc : MeOH, 1 : 1 : 0.02) to afford the tetra-aldehyde **113** as a white solid (670 mg, 70%); *R_f* 0.26 (hexanes : EtOAc : MeOH, 1 : 1 : 0.2); m.p. 142 - 144 °C (EtOAc) (lit. m.p. 143 - 145 °C); IR (film) 2935, 2856, 1719, 1449 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 9.51 (s, 4H, CHO), 1.79 (s, 12H, CH₂); ¹³C NMR (75 MHz, CDCl₃) δ 201.8, 44.8, 33.7; MS (EI) *m/z* 248 (M⁺); HRMS (EI) *m/z* calc for C₁₄H₁₆O₄ 248.1049, found: 248.1054.



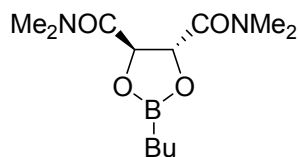
114

Tetra-methyl ester 114. To a cooled ($-78\text{ }^{\circ}\text{C}$) stirring solution of 18-crown-6 (2.80 g, 10.6 mmol) and bis(2,2,2-trifluoroethyl) (methoxycarbonylmethyl)phosphonate (762 mg, 2.40 mmol) in THF (3 mL) was added $\text{KN}(\text{TMS})_2$ (0.5 M solution in toluene, 4.26 mL, 2.13 mmol) dropwise. The resulting solution was stirred for 30 min before the tetra-aldehyde **113** (66 mg, 0.266 mmol) in THF (4 mL) was added. The reaction mixture was allowed to warm up to $-20\text{ }^{\circ}\text{C}$ during a period of 2.5 h, before it was quenched with saturated aqueous NH_4Cl (5 mL). The aqueous layer was extracted with EtOAc (3 x 8 mL), before the combined organic layers were washed with brine, dried over MgSO_4 , filtered and concentrated *in vacuo*. Purification of the residue by flash chromatography (hexanes : EtOAc, 8 : 1) gave the tetra-methyl ester **114** as a thick oil (80 mg, 64%): R_f 0.57 (hexanes : EtOAc, 2 : 1); IR (film) 2951, 2920, 1726 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 5.85 (d, $J = 13.1$ Hz, 4H, $\text{CH}=\text{CHCO}_2\text{Me}$), 5.70 (d, $J = 13.1$ Hz, 4H, $\text{CH}=\text{CHCO}_2\text{Me}$), 3.72 (s, 12H, OCH_3), 1.97 (s, 12H, CH_2); ^{13}C NMR (75 MHz, CDCl_3) δ 166.8, 153.6, 119.3, 51.4, 42.0, 37.8; MS (EI) m/z 472 (M^+); HRMS (EI) m/z calc for $\text{C}_{26}\text{H}_{32}\text{O}_8$ 472.2097, found: 472.2101.



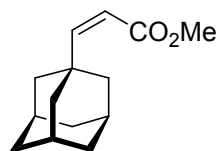
91

Tetra-ol 91. To a stirred solution of tetra-methyl ester **114** (79 mg, 0.167 mmol) in CH₂Cl₂ (3 mL) at -78°C was added DIBAL-H (1.0 M in hexanes, 1.67 mL, 1.67 mmol) dropwise over 5 min. The reaction mixture was stirred at -78°C for 1 h, and then carefully quenched by the addition of saturated aqueous NH₄Cl (0.30 mL), *i*-PrOH (5 mL), silica gel (0.2 g) and Celite (0.2 g). The mixture was allowed to warm to room temperature and filtered. The residue was washed with CH₂Cl₂/*i*-PrOH (2:1). Rotary evaporation and chromatography (CH₂Cl₂ : MeOH, 16 : 1 $\rightarrow$ 12 : 1) gave the tetra-allylic alcohol **91** (78 mg, 98%) as a solid. Colourless crystals of **91** were obtained by crystallisation from MeOH/toluene (1:1) at 4°C : R_f 0.25 (CH₂Cl₂ : MeOH, 8 : 1); m.p. $114 - 116^{\circ}\text{C}$ (MeOH : toluene, 1 : 1); IR (film) 3556, 2922, 2851 cm^{-1} ; ^1H NMR (300 MHz, MeOH-*d*₄) δ 5.41 (dt, $J = 12.4, 6.2$ Hz, 4H, CH=CHCH₂OH), 5.22 (d, $J = 12.4$ Hz, 4H, CH=CHCH₂OH), 4.30 (dd, $J = 6.2, 1.5$ Hz, 8H, CH₂OH), 1.65 (s, 12H, CH₂); ^{13}C NMR (75 MHz, MeOH-*d*₄) δ 141.0, 131.2, 60.5, 48.2, 39.8; MS (CI, NH₃) m/z 378 ($M + \text{NH}_4^+$); Unable to obtain HRMS by EI, CI or FAB. Anal. calc for C₂₂H₃₂O₄: C, 76.44; H, 7.90. Found: C, 76.37; H, 8.03; Crystal data: C₂₂H₃₂O₄, $M = 360.48$, monoclinic $P2(1)$, $a = 7.2942$ (7) Å, $b = 11.5286$ (12) Å, $c = 11.5044$ (10) Å, $\alpha, \gamma = 90^{\circ}$, $\beta = 92.841^{\circ}$, $V = 966.24$ (16) Å³, $Z = 2$, $D_c = 1.239$ mg/m³, $\mu(\text{Cu K}\alpha) = 0.665$ mm⁻¹, $T = 173$ (2) K, colourless needles; 3459 independent measured reflections, F^2 refinement, $R_1 = 0.0395$, $wR_2 = 0.0797$, 2904 independent observed reflections [$F > 4\sigma(F)$], 252 parameters. Additional crystal data can be found in **Appendix 1**.



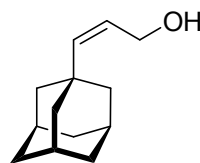
118

2-Butyl-[1,3,2]-dioxaborolane-(4*R*, 5*R*)-dicarboxylic acid bisdimethylamide 118.⁵⁷ To a solution of (+)-*N,N,N',N'*-tetramethyltartaric acid diamide (8.0 g, 39.2 mmol) in toluene (28 mL) was added 1-butaneboronic acid (4.80 g, 47.1 mmol). The mixture was heated under reflux using a Dean-Stark apparatus for 16 h to remove water produced in the reaction. The reaction mixture was allowed to cool to room temperature and concentrated *in vacuo*. The residue was dissolved in a minimal amount of CH₂Cl₂ (5 mL), filtered to remove excess 1-butaneboronic acid, and concentrated *in vacuo* to produce 10.7 g (99%) of the desired dioxaborolane **118**: $[\alpha]_D^{22}$ -99.3 (*c* 1.70, CHCl₃); IR (film) 2931, 1646, 1382 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 5.45 (s, 2H, *CH*), 3.13 (s, 6H, NCH₃), 2.91 (s, 6H, NCH₃), 1.37-1.20 (m, 4H, CH₂CH₂CH₂CH₃), 0.82-0.76 (m, 5H, CH₂CH₂CH₂CH₃); ¹³C NMR (75 MHz, CDCl₃) δ 168.2, 75.5, 36.9, 35.7, 25.6, 25.0, 13.6, 9.8; MS (EI) *m/z* 270 (M⁺); HRMS (EI) *m/z* calc for C₁₂H₂₃N₂O₄B (M⁺) 270.1751, found: 270.1754; Anal. Calc for C₁₂H₂₃N₂O₄B: C, 53.35; H, 8.58; N, 10.37. Found: C, 53.43; H, 8.46; N, 10.37. All spectroscopic data were consistent with the literature.⁵⁷



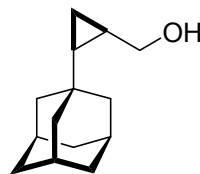
123

Methyl ester 123. To a cooled ($-78\text{ }^{\circ}\text{C}$) stirring solution of 18-crown-6 (4.83 g, 18.3 mmol) and bis(2,2,2-trifluoroethyl) (methoxycarbonylmethyl) phosphonate (1.28 g, 4.02 mmol) in THF (4 mL) was added $\text{KN}(\text{TMS})_2$ (0.5 M solution in toluene, 7.32 mL, 3.66 mmol) dropwise. The resulting solution was stirred at $-78\text{ }^{\circ}\text{C}$ for 30 min before the aldehyde **122** (300 mg, 1.83 mmol, low solubility in THF) in THF (10 mL) was added. The reaction mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for 1 h, at $0\text{ }^{\circ}\text{C}$ for 2 h and at room temperature for 2 h before it was quenched with saturated aqueous NH_4Cl (20 mL). The aqueous layer was extracted with EtOAc (3 x 25 mL), before the combined organic layers were washed with brine (30 mL), dried over MgSO_4 , filtered and concentrated *in vacuo*. Purification of the residue by chromatography (hexanes : EtOAc, 50 : 1) gave the methyl ester **123** as a colourless oil (116 mg, 30%); R_f 0.46 (hexanes : EtOAc, 15 : 1); IR (film) 2904, 2849, 1729, 1194 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 5.78 (d, $J = 13.2\text{ Hz}$, 1H, $\text{CH}=\text{CHCO}_2\text{Me}$), 5.65 (d, $J = 13.2\text{ Hz}$, 1H, $\text{CH}=\text{CHCO}_2\text{Me}$), 3.72 (s, 3H, OCH_3), 1.98 (s, 3H, adamantane methine), 1.86 (d, $J = 2.1\text{ Hz}$, 6H, CH_2), 1.71 (s, 6H, CH_2); ^{13}C NMR (75 MHz, CDCl_3) δ 167.4, 155.1, 117.9, 51.3, 40.9, 36.6, 36.2, 28.5; MS (EI) m/z 220 (M^+); HRMS (EI) m/z calc for $\text{C}_{14}\text{H}_{20}\text{O}_2$ 220.1463, found: 220.1462.



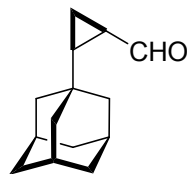
124

Allylic alcohol 124. To a solution of vinyl ester **123** (102 mg, 0.464 mmol) in CH_2Cl_2 (5 mL) at $-78\text{ }^\circ\text{C}$ was added DIBAL-H (1.0 M in hexanes, 1.16 mL, 1.16 mmol) dropwise. The reaction mixture was stirred at $-78\text{ }^\circ\text{C}$ for 40 min, then quenched by the addition of the saturated aqueous NH_4Cl (2 mL) and 4 M aqueous HCl (1 mL). The aqueous layer was extracted with EtOAc (3 x 10 mL), before the combined organic layers were washed with a saturated aqueous NaHCO_3 (20 mL) and then brine (20 mL), dried over MgSO_4 , filtered and concentrated *in vacuo*. Purification of the residue by chromatography (hexanes : EtOAc, 4 : 1) gave the allylic alcohol **124** as a colourless oil (79 mg, 90%): R_f 0.58 (hexanes : EtOAc, 2 : 1); IR (film) 3560, 2920, 2854 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 5.35 (dt, $J = 12.3, 6.2$ Hz, 1H, $\text{CH}=\text{CHCH}_2\text{OH}$), 5.17 (d, $J = 12.3$ Hz, 1H, $\text{CH}=\text{CHCH}_2\text{OH}$), 4.33 (d, $J = 6.2$ Hz, 2H, CH_2OH), 1.95 (s, 3H, adamantane methine), 1.84 (s, 1H, CH_2OH), 1.72 (s, 6H, CH_2), 1.68 (s, 6H, CH_2); ^{13}C NMR (75 MHz, CDCl_3) δ 142.0, 127.4, 59.5, 42.8, 36.6, 35.9, 28.5.



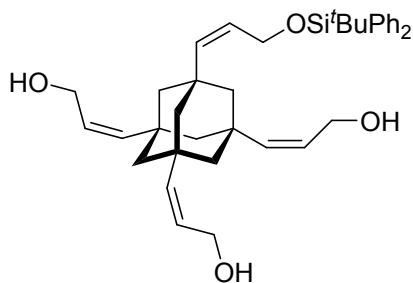
125

Cyclopropane 125. A flame-dried flask was charged with CH_2Cl_2 (3 mL) and 1,2-dimethoxyethane (0.182 mL, 1.75 mmol). The solution was cooled to $-15\text{ }^\circ\text{C}$ with an acetone/ice bath, and neat Et_2Zn (0.179 mL, 1.75 mmol) was added. To this stirred solution was added diiodomethane (0.282 mL, 3.50 mmol) slowly to keep the internal temperature below $-10\text{ }^\circ\text{C}$. After the addition was complete, the resulting clear colourless solution was stirred for an additional 10 min at $-10\text{ }^\circ\text{C}$. A solution of dioxaborolane ligand **118** (189 mg, 0.70 mmol) in CH_2Cl_2 (2 mL) was added slowly while maintaining the internal temperature below $-5\text{ }^\circ\text{C}$. A solution of allylic alcohol **124** (112 mg, 0.583 mmol) in CH_2Cl_2 (2 mL) was immediately added to the above solution. The cooling bath was removed and the reaction mixture was stirred at room temperature for 5 h. The reaction was quenched with saturated aqueous NH_4Cl (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL), before the combined organic layers were washed with brine (20 mL), dried over MgSO_4 , filtered and concentrated *in vacuo*. Purification of the residue by chromatography (hexanes : EtOAc, 7 : 1 $\rightarrow$ 6 : 1) gave the cyclopropane **125** as colourless needle crystals (104 mg, 87%): m.p. $88 - 90\text{ }^\circ\text{C}$ (hexanes : EtOAc, 2 : 1); R_f 0.57 (hexanes : EtOAc, 2 : 1); IR (film) 3271 broad, 2891, 2847, 1447 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 3.74 (m, 2H, CH_2OH), 1.94 (s, 3H, adamantane methine), 1.60-1.71 (m, 6H, adamantane methylene), 1.53 (s, 6H, adamantane methylene), 0.98-1.11 (m, 1H, CHCH_2OH), 0.59 (m, 2H, cyclopropane CH_2), 0.25 (m, 1H, cyclopropane CH); ^{13}C NMR (75 MHz, CDCl_3) δ 63.6, 43.2, 37.0, 32.3, 29.7, 28.8, 19.8, 4.5; MS (CI, NH_3) m/z 224 ($\text{M} + \text{NH}_4^+$); HRMS (CI, NH_3) m/z calc for $\text{C}_{14}\text{H}_{26}\text{NO}$ ($\text{M} + \text{NH}_4^+$) 224.2014, found: 224.2022.



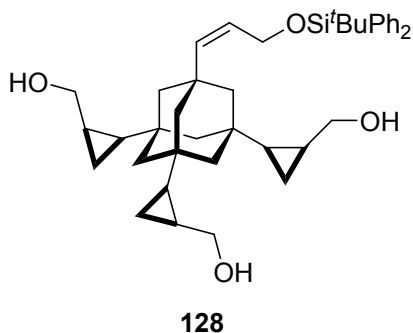
126

Aldehyde 126. To a solution of alcohol **125** (100 mg, 0.485 mmol) in CH_2Cl_2 (5 mL) was added Dess-Martin periodinane (268 mg, 0.631 mmol). The reaction mixture was stirred at room temperature for 1.2 h, then quenched by addition of saturated aqueous NaHCO_3 (3 mL) and saturated aqueous $\text{Na}_2\text{S}_2\text{O}_3$ (3 mL). The mixture was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were washed with brine (20 mL), dried over MgSO_4 , filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (hexanes : EtOAc, 14 : 1) to afford the aldehyde **126** as a colourless oil (71 mg, 72%); R_f 0.68 (hexanes : EtOAc, 4 : 1); IR (film) 2902, 2847, 1698 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 9.29 (d, $J = 7.2$ Hz, 1H, CHO), 1.97 (s, 3H, adamantane methine), 1.59-1.76 (m, 6H, adamantane methylene), 1.53 (s, 6H, adamantane methylene), 1.16-1.35 (m, 4H, cyclopropane); ^{13}C NMR (75 MHz, CDCl_3) δ 200.9, 43.2, 38.0, 36.6, 32.4, 30.2, 28.5, 9.9; MS (EI) m/z 204 (M^+); HRMS (EI) m/z calc for $\text{C}_{14}\text{H}_{20}\text{O}$ (M^+) 204.1514, found: 204.1521.



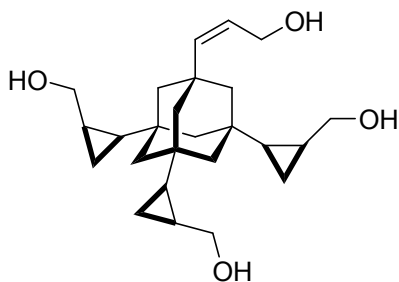
127

Mono-protected tetra-ol 127. To a stirred solution of tetra-allylic alcohol **91** (217 mg, 0.603 mmol) in dry pyridine (5 mL) was added DMAP (30 mg, 0.241 mmol) and t -BuPh₂SiCl (0.173 mL, 0.663 mmol). The reaction mixture was stirred at room temperature for 41 h before it was quenched with saturated aqueous NH₄Cl (3 mL). The aqueous layer was extracted with CH₂Cl₂/*i*-PrOH (4:1) (4 x 10 mL). The combined organic layers were dried over MgSO₄, filtered and concentrated *in vacuo*. Purification of the residue by chromatography (CH₂Cl₂ : MeOH, 16 : 1 → 12 : 1) recovered 71 mg (33%) of starting material **91** and gave the mono-silylated product **127** as a thick oil (160 mg, 44%): *R_f* 0.48 (CH₂Cl₂ : MeOH, 8 : 1); IR (film) 3350, 2928, 2855 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.69 (d, *J* = 7.2 Hz, 4H, Ar*H*), 7.42 (m, 6H, Ar*H*), 5.50 (dt, *J* = 12.3, 5.8 Hz, 1H, CH=CHCH₂OSi), 5.39 (dt, *J* = 12.2, 6.0 Hz, 3H, CH=CHCH₂OH), 5.15 (d, *J* = 12.2 Hz, 3H, CH=CHCH₂OH), 5.10 (d, *J* = 12.3 Hz, 1H, CH=CHCH₂OSi), 4.37 (d, *J* = 6.0 Hz, 6H, CH=CHCH₂OH), 4.20 (d, *J* = 5.8 Hz, 2H, CH=CHCH₂OSi), 1.73 (s, 3H, CH=CHCH₂OH), 1.52 (m, 6H, adamantane methylene), 1.44 (s, 6H, adamantane methylene), 1.05 (s, 9H, *tert*-butyl); ¹³C NMR (75 MHz, CDCl₃) δ 140.0, 137.9, 135.6, 133.7, 129.7, 129.4, 128.4, 127.7, 60.9, 59.3, 46.0, 45.9, 37.6, 29.7, 26.7, 19.1; Unable to obtain MS data.



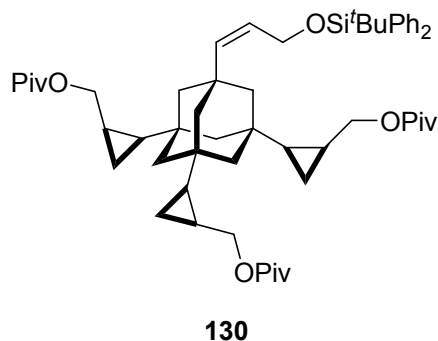
Tri-cyclopropane 128. A flame-dried flask was charged with CH_2Cl_2 (8 mL) and 1,2-dimethoxyethane (0.64 mL, 6.17 mmol). The solution was cooled to $-15\text{ }^\circ\text{C}$ with an acetone/ice bath, and neat Et_2Zn (0.63 mL, 6.17 mmol) was added. To this stirred solution was added diiodomethane (0.99 mL, 12.3 mmol) slowly to keep the internal temperature below $-10\text{ }^\circ\text{C}$. After the addition was complete, the resulting clear colourless solution was stirred for an additional 10 min at $-10\text{ }^\circ\text{C}$. A solution of the dioxaborolane ligand **118** (500 mg, 1.85 mmol) in CH_2Cl_2 (3 mL) was added slowly while maintaining the internal temperature below $-5\text{ }^\circ\text{C}$. Then a solution of mono-protected tetra-allylic alcohol **127** (308 mg, 0.514 mmol) in CH_2Cl_2 (4 mL) was immediately added to the above solution. The cooling bath was removed and the reaction mixture was stirred at room temperature for 4 h. The reaction was quenched with saturated aqueous NH_4Cl (8 mL). The aqueous layer was extracted with $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (7:1) (4 x 10 mL), before the combined organic layers were washed with brine (20 mL), dried over MgSO_4 , filtered and concentrated *in vacuo*. Purification of the residue by chromatography (hexanes : EtOAc : MeOH, 1 : 1 : 0.03 $\rightarrow$ 1 : 1 : 0.05) gave the title compound **128** as a colourless oil (295 mg, 90%): R_f 0.40 (hexanes: EtOAc: MeOH, 1 : 1 : 0.2); $[\alpha]_D^{22} -15.3$ (c 0.96, CHCl_3); IR (film) 3366 broad, 2928, 2895, 2855, 1427 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 7.70 (d, $J = 7.3$ Hz, 4H, ArH), 7.41 (m, 6H, ArH), 5.48 (dt, $J = 12.4, 5.5$ Hz, 1H, $\text{CH}=\text{CHCH}_2\text{OSi}$), 5.12 (d, $J = 12.4$ Hz, 1H, $\text{CH}=\text{CHCH}_2\text{OSi}$), 4.37 (d, $J = 5.5$ Hz, 2H, $\text{CH}=\text{CHCH}_2\text{OSi}$), 3.78 (dd, $J = 11.0, 7.5$ Hz, 3H, CH_2OH), 3.50 (dd, $J = 11.0, 8.6$ Hz, 3H, CH_2OH), 2.03 (s, 3H, CH_2OH), 1.24 (s, 6H, adamantane methylene), 1.17 (s, 6H, adamantane methylene), 1.05 (s, 9H, *tert*-butyl), 1.00 (m, 3H, cyclopropane methine), 0.55 (m, 6H, cyclopropane methylene), 0.16 (m, 3H, cyclopropane methine); ^{13}C NMR (75 MHz, CDCl_3) δ 138.8, 135.6, 133.8, 129.6, 128.8, 127.6, 63.3, 61.1, 46.9, 46.7, 37.8, 34.2, 28.9, 26.7, 19.2, 19.1, 4.6; MS (CI,

NH₃) m/z 658 (M + NH₄⁺); Unable to obtain HRMS data; Anal. calc for C₄₁H₅₆O₄Si: C, 76.83; H, 8.81. Found: C, 76.77; H, 8.90.

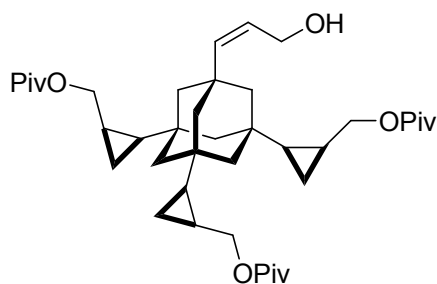


129

Tri-cyclopropane 129. To a stirred solution of protected allylic alcohol **128** (136 mg, 0.212 mmol) in THF (3 mL) at room temperature was added TBAF (1.0 M in THF, 0.233 mL, 0.233 mmol) dropwise. The reaction mixture was stirred at room temperature for 24 h before it was quenched with H₂O (2 mL). The aqueous layer was extracted with CH₂Cl₂/*i*-PrOH (4:1) (4 x 5 mL), before the combined organic layers were washed with brine (10 mL), dried over MgSO₄, filtered and concentrated *in vacuo*. Purification of the residue by chromatography (hexanes : EtOAc : MeOH, 1 : 1 : 0.2) gave the free allylic alcohol **129** as a colourless oil (79 mg, 94%): *R*_f 0.32 (CH₂Cl₂ : MeOH, 8 : 1); [α]_D²² -16.2 (*c* 1.03, MeOH); IR (film) 3345 broad, 2995, 2895 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 5.33 (dt, *J* = 12.4, 6.0 Hz, 1H, CH=CHCH₂OH), 5.17 (d, *J* = 12.4 Hz, 1H, CH=CHCH₂OH), 4.26 (dd, *J* = 6.0, 1.4 Hz, 2H, CH=CHCH₂OH), 3.75-3.62 (m, 6H, cyclopropyl CH₂OH), 1.41 (s, 6H, adamantane methylene), 1.27 (s, 6H, adamantane methylene), 1.03 (m, 3H, cyclopropane), 0.67-0.60 (m, 6H, cyclopropane), 0.26 (m, 3H, cyclopropane); ¹³C NMR (75 MHz, CDCl₃) δ 141.9, 130.6, 64.6, 60.7, 49.3, 40.1, 36.5, 31.0, 21.3, 6.4; Unable to obtain MS data.

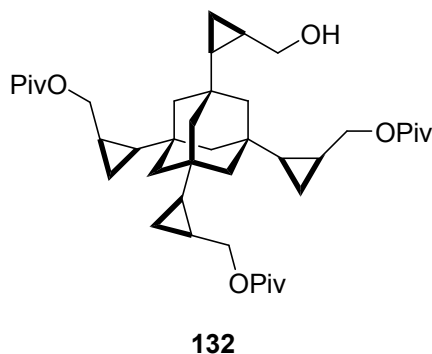


Tri-pivalate 130. To a stirred solution of tri-cyclopropane **128** (121 mg, 0.189 mmol) in dry pyridine (4 mL) was added trimethylacetyl chloride (0.233 mL, 1.89 mmol). The reaction mixture was stirred at room temperature for 2 h before it was quenched with saturated aqueous NH_4Cl (4 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL), before the combined organic layers were washed with brine (15 mL), dried over MgSO_4 , filtered and concentrated *in vacuo*. Purification of the residue by chromatography (hexanes : EtOAc, 25 : 1 $\rightarrow$ 20 : 1) gave the title tri-pivalate **130** as a colourless thick oil (160 mg, 95%): R_f 0.32 (hexanes : EtOAc, 10 : 1); $[\alpha]_D^{22} -24.5$ (c 1.02, CHCl_3); IR (film) 3069, 2967, 2932, 1726 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 7.68 (d, $J = 7.1$ Hz, 4H, ArH), 7.39 (m, 6H, ArH), 5.45 (dt, $J = 12.4, 5.6$ Hz, 1H, $\text{CH}=\text{CHCH}_2\text{OSi}$), 5.05 (d, $J = 12.4$ Hz, 1H, $\text{CH}=\text{CHCH}_2\text{OSi}$), 4.42-4.36 (m, 5H, $\text{CH}=\text{CHCH}_2\text{OSi}$ and CH_2OPiv), 3.83 (dd, $J = 11.1, 9.0$ Hz, 3H, CH_2OPiv), 1.24 (m, 12H, adamantane methylene), 1.21-1.16 (m, 30H, $\text{COC}(\text{CH}_3)_3$ and cyclopropane methine), 1.05 (s, 9H, $\text{SiC}(\text{CH}_3)_3$), 0.57 (m, 6H, cyclopropane methylene), 0.19 (m, 3H, cyclopropane methine); ^{13}C NMR (75 MHz, CDCl_3) δ 178.5, 138.4, 135.5, 133.7, 129.6, 128.8, 127.6, 65.6, 61.0, 46.9, 46.4, 38.6, 38.0, 34.2, 28.8, 27.3, 26.8, 19.1, 15.5, 4.7; Unable to obtain MS data.

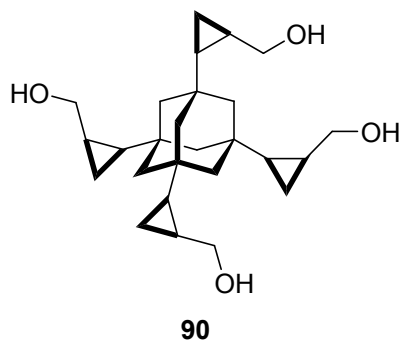


131

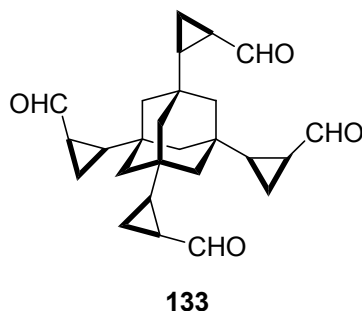
Tri-cyclopropane 131. To a stirred solution of protected allylic alcohol **130** (70 mg, 0.078 mmol) in THF (2 mL) at room temperature was added TBAF (1.0 M in THF, 0.086 mL, 0.086 mmol) dropwise. The reaction mixture was stirred at room temperature for 16 h before it was quenched with H₂O (2 mL). The aqueous layer was extracted with CH₂Cl₂ (3 x 6 mL), and the combined organic layers were washed with brine, dried over MgSO₄, filtered and concentrated *in vacuo*. Purification of the residue by chromatography (hexanes : EtOAc, 7 : 1 → 4 : 1) gave the free allylic alcohol **131** as a colourless thick oil (49 mg, 95%): *R_f* 0.15 (hexanes : EtOAc, 4 : 1); [α]_D²² -31.2 (*c* 1.60, CHCl₃); IR (film) 3516 broad, 2971, 2906, 1726, 1480, 1283 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 5.39 (dt, *J* = 12.3, 6.5 Hz, 1H, CH=CHCH₂OH), 5.17 (d, *J* = 12.3 Hz, 1H, CH=CHCH₂OH), 4.44 (dd, *J* = 11.5, 7.5 Hz, 3H, CH₂OPiv), 4.26 (d, *J* = 6.5 Hz, 2H, CH=CHCH₂OH), 3.92 (dd, *J* = 11.5, 8.9 Hz, 3H, CH₂OPiv), 1.35 (s, 6H, adamantane methylene), 1.31-1.29 (m, 6H, adamantane methylene), 1.22 (s, 27H, COC(CH₃)₃), 1.11 (m, 3H, cyclopropane methine), 0.64 (m, 6H, cyclopropane methylene), 0.27 (m, 3H, cyclopropane methine); ¹³C NMR (75 MHz, CDCl₃) δ 178.7, 140.3, 128.2, 65.7, 59.2, 47.3, 46.3, 38.7, 37.8, 34.3, 28.9, 27.3, 15.5, 4.7; Unable to obtain MS data.



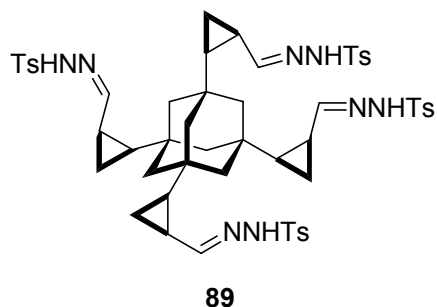
Tetra-cyclopropane 132. A flame-dried flask was charged with CH_2Cl_2 (4 mL) and 1,2-dimethoxyethane (0.196 mL, 1.89 mmol). The solution was cooled to $-15\text{ }^\circ\text{C}$ with an acetone/ice bath, and neat Et_2Zn (0.193 mL, 1.89 mmol) was added. To this stirred solution was added diiodomethane (0.304 mL, 3.77 mmol) slowly to keep the internal temperature below $-10\text{ }^\circ\text{C}$. After the addition was complete, the resulting clear colourless solution was stirred for an additional 10 min at $-10\text{ }^\circ\text{C}$. A solution of the dioxaborolane ligand **118** (153 mg, 0.566 mmol) in CH_2Cl_2 (1 mL) was added slowly while maintaining the internal temperature below $-5\text{ }^\circ\text{C}$. Then 2 mL of the above prepared solution was immediately added to allylic alcohol **131** (103 mg, 0.157 mmol) in CH_2Cl_2 (1 mL) at $-10\text{ }^\circ\text{C}$. The cooling bath was removed and the reaction mixture was stirred at room temperature for 5 h. The reaction was quenched with saturated aqueous NH_4Cl (2 mL). The aqueous layer was extracted with $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (6:1) (4 x 5 mL), before the combined organic layers were washed with brine (10 mL), dried over MgSO_4 , filtered and concentrated *in vacuo*. Purification of the residue by chromatography (hexanes : EtOAc , 15 : 1 $\rightarrow$ 12 : 1) gave the title compound **132** as a colourless oil (66 mg, 63%): R_f 0.24 (hexanes: EtOAc , 4 : 1); $[\alpha]_D^{22} -25.3$ (c 1.02, CHCl_3); IR (film) 3524 broad, 2969, 1726, 1152 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 4.40 (m, 3H, CH_2OPiv), 3.92 (m, 3H, CH_2OPiv), 3.82 (dd, $J = 10.8$, 7.3 Hz, 1H, CH_2OH), 3.60 (dd, $J = 10.8$, 7.9 Hz, 1H, CH_2OH), 1.39-1.09 (m, 42H, adamantane methylene and $\text{COC}(\text{CH}_3)_3$ and CHCH_2OPiv), 0.87 (m, 1H, CHCH_2OH), 0.64-0.60 (m, 8H, cyclopropane methylene), 0.27-0.21 (m, 4H, cyclopropane methine); ^{13}C NMR (75 MHz, CDCl_3) δ 178.6, 65.7, 63.3, 47.7, 46.6, 38.7, 34.3, 28.9, 27.3, 19.4, 15.5, 4.7; MS (CI, NH_3) m/z 686 ($\text{M} + \text{NH}_4^+$); HRMS (CI, NH_3) m/z calc for $\text{C}_{41}\text{H}_{68}\text{NO}_7$ ($\text{M} + \text{NH}_4^+$) 686.4996, found: 686.5004.



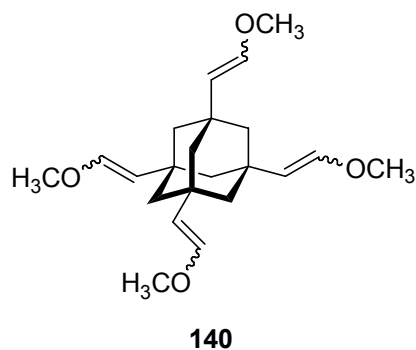
Tetra-cyclopropane 90. To a stirred solution of tri-pivalate **132** (63 mg, 0.094 mmol) in CH_2Cl_2 (3.5 mL) at -78°C was added DIBAL-H (1.0 M in hexanes, 0.706 mL, 0.706 mmol) dropwise over 5 min. After the reaction mixture was stirred at -78°C for 1 h, saturated aqueous NH_4Cl (0.14 mL), *i*-PrOH (4 mL), silica gel (200 mg) and Celite (200 mg) were added. The mixture was allowed to warm to room temperature and filtered, and the residue was washed with $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (4:1). Rotary evaporation and chromatography (CH_2Cl_2 : MeOH, 16 : 1 $\rightarrow$ 12 : 1) gave the tetra-*syn*-cyclopropane **90** (35 mg, 89%) as a viscous oil. Colourless crystals of tetra-*syn*-cyclopropane **90** were obtained by crystallisation from MeOH/toluene/THF (1:1:1): m.p. $168 - 170^\circ\text{C}$ (MeOH : toluene : THF, 1 : 1 : 1); R_f 0.32 (CH_2Cl_2 : MeOH, 8 : 1); $[\alpha]_D^{25} -17.6$ (c 1.0, MeOH); IR (film) 3321 broad, 2894, 2360 cm^{-1} ; ^1H NMR (300 MHz, MeOH- d_4) δ 3.72 (m, 8H, CH_2OH), 1.27 (s, 12H, adamantane methylene), 1.03 (m, 4H, cyclopropane methine), 0.70-0.63 (m, 8H, cyclopropane methylene), 0.29 (d, $J = 3.4$ Hz, 4H, cyclopropane methine); ^{13}C NMR (75 MHz, MeOH- d_4) δ 64.6, 49.6, 36.6, 31.0, 21.2, 6.4; MS (CI, NH_3) m/z 434 ($\text{M} + \text{NH}_4^+$); Unable to obtain HRMS; Crystal data: $\text{C}_{26}\text{H}_{40}\text{O}_4$, $M = 416.58$, monoclinic $C2$, $a = 22.4705$ (19) $\text{\AA}$, $b = 10.5816$ (10) $\text{\AA}$, $c = 9.5532$ (12) $\text{\AA}$, $\alpha, \gamma = 90^\circ$, $\beta = 96.483^\circ$, $V = 2257.0$ (4) $\text{\AA}^3$, $Z = 4$, $D_c = 1.226$ mg/m^3 , $\mu(\text{Cu K}\alpha) = 0.080$ mm^{-1} , $T = 173$ (2) K, colourless plates; 6144 independent measured reflections, F^2 refinement, $R_1 = 0.0996$, $wR_2 = 0.2330$, 2993 independent observed reflections [$F > 4\sigma(F)$], 293 parameters. Additional crystal data can be found in **Appendix 2**.



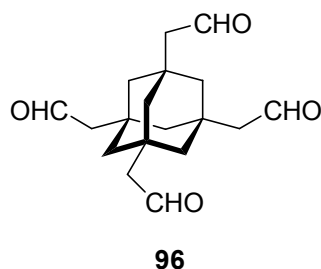
Tetra-aldehyde 133. A solution of oxalyl chloride (19 μL , 0.224 mmol) in CH_2Cl_2 (1 mL) was cooled to $-78\text{ }^\circ\text{C}$. Under vigorous stirring, DMSO (32 μL , 0.448 mmol) was added slowly, and the reaction mixture was stirred at this temperature for an additional 15 min. A solution of tetra-cyclopropane **90** (11 mg, 0.0264 mmol) in a mixture of DMSO (0.3 mL) and CH_2Cl_2 (0.6 mL) was added slowly, and the reaction mixture was stirred at $-78\text{ }^\circ\text{C}$ for an additional 1 hour. After this, triethylamine (0.15 mL) was added dropwise, and the mixture was allowed to warm up to room temperature. Water (5 mL) and CH_2Cl_2 (5 mL) were added and the two phases were separated. The organic phase was washed with 5% aqueous HCl (2 mL), water (2 mL), 5% aqueous NaHCO_3 (4 mL) and brine (4 mL), dried over MgSO_4 , filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (hexanes : EtOAc : MeOH, 1 : 1 : 0.04) to afford the tetra-aldehyde **133** as a white solid (8 mg, 82%): m.p. $121 - 123\text{ }^\circ\text{C}$ (hexanes : EtOAc, 1 : 2); R_f 0.35 (hexanes : EtOAc : MeOH, 1 : 1 : 0.2); $[\alpha]_D^{22} -73.1$ (c 1.03, CHCl_3); IR (film) 2924, 2849, 1692 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 9.33 (d, $J = 6.1\text{ Hz}$, 4H, CHO), 1.87-1.77 (m, 4H, cyclopropane), 1.33-1.10 (m, 12H, cyclopropane), 1.20 (s, 12H, adamantane methylene); ^{13}C NMR (75 MHz, CDCl_3) δ 200.0, 46.9, 36.5, 34.9, 29.6, 9.9; Unable to obtain MS data; Anal. calc for $\text{C}_{26}\text{H}_{32}\text{O}_4$: C, 76.44; H, 7.90. Found: C, 76.37; H, 8.03.



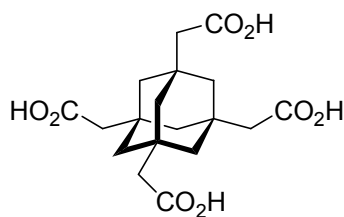
Tetra-tosylhydrazone 89. *p*-Toluenesulfonyl hydrazide hydrochloride (42 mg, 0.225 mmol) was added to a solution of tetra-aldehyde **133** (23 mg, 0.056 mmol) in MeOH (3 mL). The reaction mixture was stirred at room temperature for 4.5 h. Removal of the solvent *in vacuo* and purification of the residue by flash chromatography (hexanes : EtOAc : MeOH, 1 : 1 : 0.02) to afford tetra-tosylhydrazone **89** as a white solid (50 mg, 82%): m.p. 149 - 151 °C (hexanes : EtOAc, 1 : 2); R_f 0.31 (hexanes : EtOAc : MeOH, 1 : 1 : 0.2); $[\alpha]_D^{22}$ -154.7 (c 1.02, CHCl₃); IR (film) 3204, 2923, 2852, 1334, 1164 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 9.23-8.38 (m, 4H, CH=NNHTs), 7.97-7.89 (m, 8H, ArH), 7.35-7.28 (m, 8H, ArH), 7.08-6.98 (m, 2H, CH=NNHTs), 6.61-6.48 (m, 2H, CH=NNHTs), 2.40 (s, 12H, ArCH₃), 1.59 (bs, 4H, cyclopropane methine), 1.27 (s, 8H, cyclopropane methylene), 1.12-0.75 (m, 16H, cyclopropane methine and adamantane methylene); See **Appendix 3** for ¹³C NMR data; Unable to obtain MS data.



Tetra-enol ether 140. To a stirred suspension of $\text{Ph}_3\text{PCH}_2\text{OMeCl}$ (2.21 g, 6.45 mmol) in THF (10 mL) at $-78\text{ }^\circ\text{C}$ was added sodium bis(trimethylsilyl) amide (1.0 M in THF, 6.05 mL, 6.05 mmol). The mixture was stirred at $-78\text{ }^\circ\text{C}$ for 1 h to give a red solution. Then tetra-aldehyde **113** (200 mg, 0.806 mmol) in THF (10 mL) was added dropwise to the solution. The reaction mixture was allowed warm up to room temperature slowly and stirred for 16 h before saturated aqueous NH_4Cl (10 mL) was added. The mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (20 mL) and dried over MgSO_4 , filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (hexanes : EtOAc, 30 : 1 $\rightarrow$ 15 : 1) to afford the tetra-enol ether **140** (ca. 1 : 1 (*E*)-olefin : (*Z*)-olefin isomers) as a colourless oil (230 mg, 80%); R_f 0.62 (hexanes : EtOAc, 4 : 1); IR (film) 3019, 2930, 2901, 2849, 1656, 1449 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 6.22 (d, $J = 12.9\text{ Hz}$, 2H, (*E*)-isomer $\text{CH}=\text{CHOCH}_3$), 5.71-5.67 (m, 2H, (*Z*)-isomer $\text{CH}=\text{CHOCH}_3$), 4.72 (d, $J = 12.9\text{ Hz}$, 2H, (*E*)-isomer $\text{CH}=\text{CHOCH}_3$), 4.05 (d, $J = 7.0\text{ Hz}$, 2H, (*Z*)-isomer $\text{CH}=\text{CHOCH}_3$), 3.53 (s, 6H, (*Z*)-isomer $\text{CH}=\text{CHOCH}_3$), 3.49 (s, 6H, (*E*)-isomer $\text{CH}=\text{CHOCH}_3$), 1.72-1.69 (m, 6H, (*Z*)-isomer adamantane methylene), 1.52 (s, 6H, (*E*)-isomer adamantane methylene); See **Appendix 4** for ^{13}C NMR data; Unable to obtain MS data; Anal. Calc for $\text{C}_{22}\text{H}_{32}\text{O}_4$: C, 73.30; H, 8.95. Found: C, 73.34; H, 8.96.

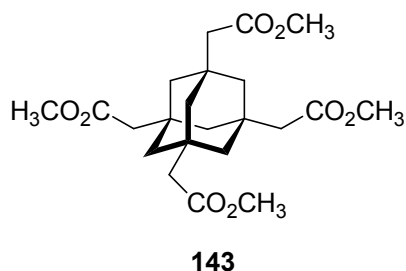


Tetra-aldehyde 96. To tetra-enol ether **140** (23 mg, 0.064 mmol) was added a solution of trifluoromethanesulfonic acid (41 mg, 0.275 mmol) in a mixed solvent system of $\text{CH}_2\text{Cl}_2/i\text{-PrOH}/\text{H}_2\text{O}$ (60:20:1) (5 mL). The mixture was stirred at room temperature for 16 h, before a saturated aqueous NaHCO_3 (8 mL) was added. The mixture was extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layers were dried over MgSO_4 , filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (hexanes : EtOAc : MeOH, 1 : 1 : 0.2) to afford tetra-aldehyde **96** (11.5 mg, 60%) as colourless crystals: m.p. 124 - 126 °C (EtOAc); R_f 0.24 (hexanes : EtOAc : MeOH, 1 : 1 : 0.2); IR (film) 2923, 2850, 1713 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 9.83 (t, $J = 2.6$ Hz, 4H, CHO), 2.28 (d, $J = 2.6$ Hz, 8H, CH_2CHO), 1.56 (s, 12H, adamantane methylene); ^{13}C NMR (100 MHz, CDCl_3) δ 201.6, 55.4, 45.6, 34.8; MS (EI) m/z 304 (M^+); HRMS (EI) m/z calc for $\text{C}_{18}\text{H}_{24}\text{O}_4$ (M^+) 304.1675, found: 304.1683; Anal. Calc for $\text{C}_{18}\text{H}_{24}\text{O}_4$: C, 71.03; H, 7.95. Found: C, 70.98; H, 7.93.



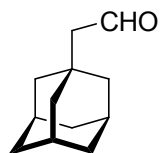
141

Tetra-carboxylic acid 141. To tetra-aldehyde **96** (52 mg, 0.171 mmol) in a flask was added *t*-BuOH (11.2 mL) and 2-methyl-2-butene (2.8 mL). A solution of NaClO₂ (308 mg, 2.74 mmol) and NaH₂PO₄·H₂O (378 mg, 2.74 mmol) in H₂O (2.8 mL) was then added slowly to the above stirred mixture at room temperature. The mixture was stirred at room temperature in the dark overnight. The mixture was acidified to pH 1-2 and extracted with EtOAc (5 x 15 mL). The combined organic layers were extracted back into saturated aqueous NaHCO₃ (70 mL). This solution was then reacidified to pH 1-2 using 4 M HCl and extracted with EtOAc (4 x 40 mL). The combined organic extracts were dried over MgSO₄, filtered, and concentrated *in vacuo*. The crude product was placed under vacuum overnight to afford the tetra-acid **141** as a white solid (52 mg, 83%). The crude product was used directly in the subsequent step without further purification: ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.96 (*br s*, 4H, CO₂H), 2.01 (*s*, 8H, CH₂CO₂H), 1.32 (*s*, 12H, adamantane methylene); ¹³C NMR (100 MHz, DMSO-*d*₆) δ 172.8, 47.7, 45.6, 34.2.



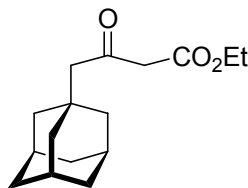
Tetra-methyl ester 143. To a solution of tetra-acid **141** (29 mg, 0.079 mmol) and DMF (1.2 μ L, 0.016 mmol) in CH_2Cl_2 (3 mL) at 0 $^\circ\text{C}$ was added SOCl_2 (35 μ L, 0.47 mmol) slowly. The mixture was stirred at room temperature overnight. All solvents were removed *in vacuo* and the crude tetra-acid chloride **142** was allowed to dry under vacuum for an additional 4 h and was used in the subsequent step without any further purification.

MeOH (6 mL) was added to the above crude tetra-acid chloride **142** in a flask. The mixture was stirred at room temperature overnight, during which time the original cloudy mixture became a clear solution. MeOH was removed *in vacuo*. The residue was dissolved in EtOAc (20 mL), washed with water (5 mL), 5% aqueous Na_2CO_3 (5 mL) and brine (10 mL). The organic extracts were dried over MgSO_4 , filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (hexanes : EtOAc, 4 : 1) to afford tetra-methyl ester **143** as colourless crystals (14 mg, 42% over two steps): m.p. 80 - 82 $^\circ\text{C}$ (hexanes : EtOAc, 1 : 1); R_f 0.31 (hexanes : EtOAc, 2 : 1); IR (film) 2951, 2924, 2851, 1732, 1438 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 3.65 (s, 12H, CO_2CH_3), 2.17 (s, 8H, $\text{CH}_2\text{CO}_2\text{CH}_3$), 1.40 (s, 12H, adamantane methylene); ^{13}C NMR (100 MHz, CDCl_3) δ 171.6, 51.2, 47.1, 45.2, 34.3; MS (EI) m/z 424 (M^+); HRMS (EI) m/z calc for $\text{C}_{22}\text{H}_{32}\text{O}_8$ 424.2097, found: 424.2083.



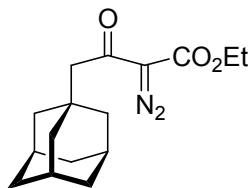
149

2-(1-Adamantyl)ethanal 149.⁶¹ A solution of oxalyl chloride (0.263 mL, 3.06 mmol) in CH₂Cl₂ (7 mL) was cooled to -78 °C. Under vigorous stirring, A solution of DMSO (1.60 mL, 22.5 mmol) in CH₂Cl₂ (2 mL) was added over 2 min, and the reaction mixture was stirred at this temperature for an additional 15 min. A solution of 1-adamantaneethanol (**148**) (500 mg, 2.78 mmol) in CH₂Cl₂ (4 mL) was added slowly, and the reaction mixture was stirred at -78 °C for 30 min. After this, triethylamine (1.95 mL) was added dropwise, and the mixture was allowed to warm up to room temperature for 1 h. Water (15 mL) was added and the two phases were separated. The organic layer was washed with 5% aqueous HCl (10 mL), water (10 mL), 5% aqueous NaHCO₃ (10 mL) and brine (10 mL), dried over MgSO₄, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (hexanes : EtOAc, 30 : 1) to afford the aldehyde **149** as a colourless oil (444 mg, 90%); *R_f* 0.44 (hexanes : EtOAc, 10 : 1); IR (film) 2902, 2848, 1720 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 9.87 (t, *J* = 3.4 Hz, 1H, CHO), 2.12 (d, *J* = 3.4 Hz, 2H, CH₂CHO), 1.98 (s, 3H, adamantane methine), 1.74-1.64 (m, 12H, adamantane methylene); ¹³C NMR (100 MHz, CDCl₃) δ 203.8, 57.2, 42.7, 36.6, 33.3, 28.4; MS (EI) *m/z* 178 (M⁺); HRMS (EI) *m/z* calc for C₁₂H₁₈O 178.1358, found: 178.1353. All spectroscopic data were consistent with the literature values.⁶¹



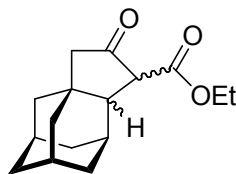
150

β-Keto ester 150. A solution of aldehyde **149** (89 mg, 0.50 mmol) in CH₂Cl₂ (2 mL) was added to a stirring mixture of anhydrous SnCl₂ (9.5 mg, 0.05 mmol) and ethyl diazoacetate (58 μL, 0.55 mmol) in CH₂Cl₂ (2 mL). After 1 h of stirring at room temperature, the mixture was washed with brine (5 mL) and extracted with CH₂Cl₂ (3 x 10 mL). The organic extracts were dried over MgSO₄, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (hexanes : EtOAc, 40 : 1) to afford the β-keto ester **150** (*ca.* 4 : 1 keto form and enol form) as a colourless oil (106 mg, 80%): *R_f* 0.44 (hexanes : EtOAc, 10 : 1); IR (film) 2903, 2848, 1744, 1715, 1630 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): (keto form) δ 4.19 (q, *J* = 7.1 Hz, 2H, CO₂CH₂CH₃), 3.41 (s, 2H, CH₂CO₂Et), 2.28 (s, 2H, CH₂COCH₂CO₂Et), 1.96 (s, 3H, adamantane methine), 1.65-1.64 (m, 12H, adamantane methylene), 1.29 (t, *J* = 7.1 Hz, 3H, CO₂CH₂CH₃); (enol form) δ 12.10 (s, 1H, HOC=CH), 4.90 (s, 1H, HOC=CH), 4.19 (q, *J* = 7.2 Hz, 2H, CO₂CH₂CH₃), 1.93 (s, 2H, CH₂C(OH)=CH), 1.72 (s, 3H, adamantane methine), 1.69-1.59 (m, 12H, adamantane methylene), 1.31 (t, *J* = 7.2 Hz, 3H, CO₂CH₂CH₃); ¹³C NMR (100 MHz, CDCl₃): (keto form) δ 202.4, 167.2, 61.3, 56.0, 51.9, 42.3, 36.8, 33.7, 28.5, 14.2; (enol form) δ 176.8, 172.6, 91.3, 59.9, 50.0, 42.6, 36.7, 33.4, 28.7, 14.3; MS (EI) *m/z* 264 (M⁺); HRMS (EI) *m/z* calc for C₁₆H₂₄O₃ 264.1725, found: 264.1717.



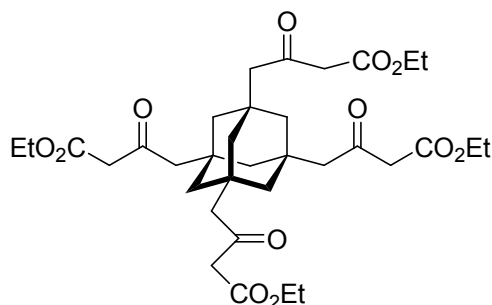
146

α -Diazo- β -keto ester 146. To a solution of the β -keto ester **150** (79 mg, 0.299 mmol) and 4-acetamidobenzenesulfonyl azide (79 mg, 0.329 mmol) in dry acetonitrile (4 mL) at 0 °C was added triethylamine (0.126 mL, 0.898 mmol) dropwise. After stirring at room temperature for 3 h, the reaction mixture was concentrated *in vacuo* and the resultant solid was triturated with diethyl ether/petroleum spirit (1:1) (60 mL). The filtrate was concentrated *in vacuo*. The residue was purified by flash chromatography (hexanes : EtOAc, 30 : 1) to afford α -diazo- β -keto ester **146** (86 mg, 99%) as a viscous oil: R_f 0.46 (hexanes : EtOAc, 10 : 1); IR (film) 2903, 2849, 2131, 1719, 1650 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 4.29 (q, J = 7.2 Hz, 2H, CO₂CH₂CH₃), 2.71 (s, 2H, CH₂COC=N₂), 1.95 (s, 3H, adamantane methine), 1.67-1.66 (m, 12H, adamantane methylene), 1.34 (t, J = 7.2 Hz, 3H, CO₂CH₂CH₃); ¹³C NMR (100 MHz, CDCl₃) δ 191.9, 161.5, 77.3, 61.3, 51.5, 42.4, 36.8, 34.7, 28.7, 14.4; MS (EI) m/z 290 (M⁺); HRMS (EI) m/z calc for C₁₆H₂₂N₂O₃ 290.1630, found: 290.1626.



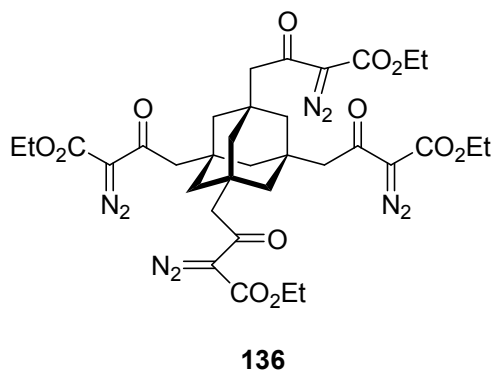
147

β -Keto ester 147. Di-rhodium tetra-acetate (1.8 mg, 4.1 μ mol) was added to a stirred solution of α -diazo- β -keto ester **146** (60 mg, 0.21 mmol) in CH_2Cl_2 (5 mL) at room temperature. The reaction was stirred at room temperature for 1.5 h, and the solvent was removed *in vacuo*. The crude product was purified by flash chromatography (hexanes : EtOAc, 25 : 1) to afford a single diastereomer β -keto ester **147** (49 mg, 90%) as a viscous oil: R_f 0.27 (hexanes : EtOAc, 10 : 1); IR (film) 2905, 2852, 1755, 1724 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 4.19 (q, $J = 7.2$ Hz, 2H, COCH_2CH_3), 3.29 (d, $J = 12.9$ Hz, 1H, CHCO_2Et), 2.52 (dd, $J = 12.9, 1.6$ Hz, 1H, $\text{COCH}(\text{CO}_2\text{Et})\text{CH}$), 2.07 (s, 2H, $\text{CH}_2\text{COCHCO}_2\text{Et}$), 2.02-1.64 (m, 11H, adamantane methylene and methine), 1.49 (s, 2H, adamantane methine), 1.27 (t, $J = 7.2$ Hz, 3H, COCH_2CH_3); ^{13}C NMR (100 MHz, CDCl_3) δ 211.1, 169.7, 61.3, 55.8, 53.2, 51.2, 43.0, 38.3, 37.9, 37.0, 35.8, 29.8, 29.1, 28.5, 27.9, 14.2; MS (EI) m/z 262 (M^+); HRMS (EI) m/z calc for $\text{C}_{16}\text{H}_{22}\text{O}_3$ 262.1569, found: 262.1566.

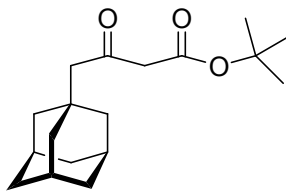


151

Tetra- β -keto ester 151. A solution of tetra-aldehyde **96** (238 mg, 0.78 mmol) in CH_2Cl_2 (6 mL) was added to a stirred mixture of anhydrous SnCl_2 (60 mg, 0.31 mmol) and ethyl diazoacetate (0.362 mL, 3.44 mmol) in CH_2Cl_2 (10 mL) at 0 °C. After 2 h of stirring at room temperature, the mixture was washed with brine (15 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The organic extracts were dried over MgSO_4 , filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (hexanes : EtOAc, 2 : 1) to afford the tetra- β -keto ester **151** (ca. 3 : 1 all keto : all enol forms) as a colourless oil (417 mg, 82%); R_f 0.46 (hexanes : EtOAc, 1 : 1); IR (film) 2983, 2905, 1744, 1714, 1633 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): (all keto form) δ 4.17 (q, $J = 7.2$ Hz, 8H, $\text{CO}_2\text{CH}_2\text{CH}_3$), 3.36 (m, 8H, $\text{CH}_2\text{CO}_2\text{Et}$), 2.34 (m, 8H, $\text{CH}_2\text{COCH}_2\text{CO}_2\text{Et}$), 1.46-1.38 (m, 12H, adamantane methylene), 1.26 (t, $J = 7.2$ Hz, 12H, $\text{CO}_2\text{CH}_2\text{CH}_3$); (all enol form) δ 12.06 (s, 4H, $\text{HOC}=\text{CH}$), 4.86 (m, 4H, $\text{HOC}=\text{CH}$), 4.17 (q, $J = 7.2$ Hz, 8H, $\text{CO}_2\text{CH}_2\text{CH}_3$), 1.97 (m, 8H, $\text{CH}_2\text{C}(\text{OH})=\text{CH}$), 1.46-1.38 (m, 12H, adamantane methylene), 1.26 (t, $J = 7.2$ Hz, 12H, $\text{CO}_2\text{CH}_2\text{CH}_3$); ^{13}C NMR (100 MHz, CDCl_3): (all keto form) δ 201.5, 166.9, 61.3, 54.1, 51.3, 44.6, 34.9, 14.1; (all enol form) δ 175.6, 172.4, 91.7, 59.9, 48.5, 45.3, 34.7, 14.2; MS (EI) m/z 648 (M^+); HRMS (EI) m/z calc for $\text{C}_{34}\text{H}_{48}\text{O}_{12}$ 648.3146, found: 648.3145; Anal. Calc for $\text{C}_{34}\text{H}_{48}\text{O}_{12}$: C, 62.95; H, 7.46. Found: C, 63.02; H, 7.52.

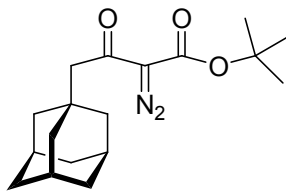


Tetra- α -diazo- β -keto ester 136. To a stirred solution of the tetra- β -ketoester **151** (402 mg, 0.62 mmol) and 4-acetamidobenzenesulfonyl azide (655 mg, 2.73 mmol) in dry acetonitrile (15 mL) at 0 °C was added triethylamine (1.04 mL, 7.44 mmol) dropwise. After stirring at room temperature for 3 h, the reaction mixture was concentrated *in vacuo* and the resultant solid was triturated with diethyl ether/petroleum spirit (1:1) (100 mL). The mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was purified by flash chromatography (hexanes : EtOAc, 2 : 1) to afford the tetra-diazo-ester **136** (450 mg, 97%) as a viscous oil: R_f 0.51 (hexanes : EtOAc, 1 : 1); IR (film) 2133, 1714, 1649, 1300 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 4.23 (q, $J = 7.2$ Hz, 8H, $\text{CO}_2\text{CH}_2\text{CH}_3$), 2.68 (s, 8H, $\text{CH}_2\text{COC}=\text{N}_2$), 1.45 (s, 12H, adamantane methylene), 1.28 (t, $J = 7.2$ Hz, 12H, $\text{CO}_2\text{CH}_2\text{CH}_3$); ^{13}C NMR (100 MHz, CDCl_3) δ 190.8, 161.2, 77.2, 61.2, 50.1, 45.2, 35.9, 14.2; MS (ES) m/z 775 ($\text{M}+\text{Na}^+$); HRMS (ES) m/z calc for $\text{C}_{34}\text{H}_{40}\text{N}_8\text{O}_{12}\text{Na}$ 775.2663, found: 775.2654.



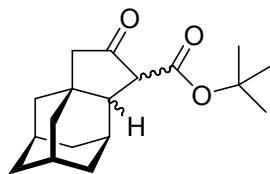
154

β-Keto ester 154. A solution of aldehyde **149** (390 mg, 2.19 mmol) in CH₂Cl₂ (6 mL) was added to a stirred mixture of anhydrous SnCl₂ (42 mg, 0.22 mmol) and *tert*-butyl diazoacetate (0.333 mL, 2.41 mmol) in CH₂Cl₂ (6 mL). After 1.5 h of stirring at room temperature, the mixture was washed with brine (15 mL) and extracted with CH₂Cl₂ (3 x 20 mL). The organic extracts were dried over MgSO₄, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (hexanes : EtOAc, 40 : 1) to afford the β-keto ester **154** (ca. 6 : 4 keto form and enol form) as a colourless oil (390 mg, 61%); *R_f* 0.41 (hexanes : EtOAc, 10 : 1); IR (film) 2902, 2848, 1739, 1714, 1637 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): (keto form) δ 3.24 (s, 2H, CH₂CO₂C(CH₃)₃), 2.19 (s, 2H, CH₂COCH₂CO₂C(CH₃)₃), 1.89 (s, 3H, adamantane methine), 1.64-1.52 (m, 12H, adamantane methylene), 1.40 (s, 9H, CH₂CO₂C(CH₃)₃); (enol form) δ 12.15 (s, 1H, HOC=CH), 4.73 (s, 1H, HOC=CH), 1.89 (s, 3H, adamantane methine), 1.83 (s, 2H, CH₂C(OH)=CH), 1.61-1.52 (m, 12H, adamantane methylene), 1.43 (t, 9H, CH₂CO₂C(CH₃)₃); ¹³C NMR (100 MHz, CDCl₃): (keto form) δ 202.9, 166.5, 81.7, 55.9, 53.1, 42.3, 36.7, 33.6, 28.5, 28.0; (enol form) δ 176.1, 172.6, 92.7, 80.6, 50.0, 42.6, 36.8, 33.3, 28.7, 28.3; MS (EI) *m/z* 292 (M⁺); HRMS (EI) *m/z* calc for C₁₈H₂₈O₃ 292.2038, found: 292.2034; Anal. Calc for C₁₈H₂₈O₃: C, 73.93; H, 9.65. Found: C, 74.01; H, 9.58.



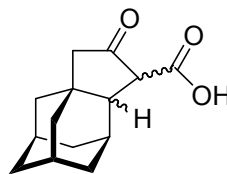
155

α -Diazo- β -keto ester 155. To a stirred solution of the β -keto ester **154** (112 mg, 0.384 mmol) and 4-acetamidobenzenesulfonyl azide (101 mg, 0.422 mmol) in dry acetonitrile (5 mL) at 0 °C was added triethylamine (0.162 mL, 1.15 mmol) dropwise. After stirring at room temperature for 4 h, the reaction mixture was concentrated *in vacuo* and the resultant solid was triturated with diethyl ether/petroleum spirit (1:1). The filtrate was concentrated *in vacuo*. The residue was purified by flash chromatography (hexanes : EtOAc, 40 : 1) to afford α -diazo- β -keto ester **155** (109 mg, 90%) as a viscous oil: R_f 0.41 (hexanes : EtOAc, 10 : 1); IR (film) 2904, 2848, 2129, 1712, 1689, 1648 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 2.66 (s, 2H, $\text{CH}_2\text{COC}(\text{N}_2)$), 1.93 (s, 3H, adamantane methine), 1.66 (m, 12H, adamantane methylene), 1.52 (s, 9H, $\text{C}(\text{CH}_3)_3$); ^{13}C NMR (100 MHz, CDCl_3) δ 192.0, 160.6, 82.9, 78.2, 51.3, 42.3, 36.7, 34.5, 28.7, 28.2; MS (EI) m/z 318 (M^+); HRMS (EI) m/z calc for $\text{C}_{18}\text{H}_{26}\text{N}_2\text{O}_3$ 318.1943, found: 318.1942; Anal. Calc for $\text{C}_{18}\text{H}_{26}\text{N}_2\text{O}_3$: C, 67.90; H, 8.23; N, 8.80. Found: C, 68.01; H, 8.27; N, 8.74.



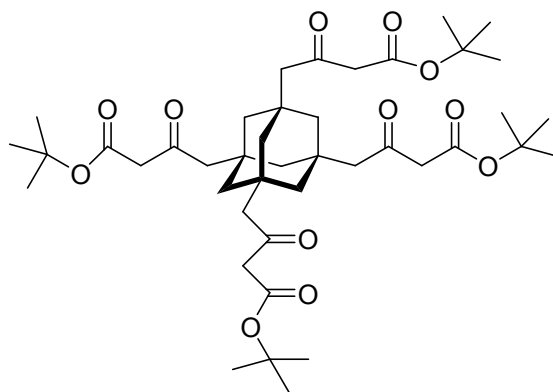
156

β-Keto ester 156. Di-rhodium tetra-acetate (14.5 mg, 0.033 mmol) was added to a stirred solution of α-diazo-β-keto ester **155** (208 mg, 0.654 mmol) in CH₂Cl₂ (10 mL) at room temperature. The reaction was stirred at room temperature for 1.5 h, and the solvent was removed *in vacuo*. The crude product was purified by flash chromatography (hexanes : EtOAc, 30 : 1) to afford β-ketoester **156** (173 mg, 91%) as a colourless viscous oil: *R_f* 0.34 (hexanes : EtOAc, 10 : 1); IR (film) 2906, 2852, 1752, 1722 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 3.18 (d, *J* = 12.9 Hz, 1H, COCHCO₂C(CH₃)₃), 2.46 (d, *J* = 12.8 Hz, 1H, COCH(CO₂C(CH₃)₃)CH), 2.06-1.67 (m, 13H, adamantane methylene and methine), 2.03 (s, 2H, CH₂COCH), 1.45 (s, 9H, C(CH₃)₃); ¹³C NMR (100 MHz, CDCl₃) δ 211.4, 168.9, 81.5, 56.7, 53.1, 51.2, 42.9, 38.3, 37.9, 37.0, 35.6, 29.7, 29.1, 28.5, 28.0, 27.8; MS (EI) *m/z* 290 (M⁺); HRMS (EI) *m/z* calc for C₁₈H₂₆O₃ 290.1882, found: 290.1881; Anal. Calc for C₁₈H₂₆O₃: C, 74.45; H, 9.02. Found: C, 74.55; H, 8.99.



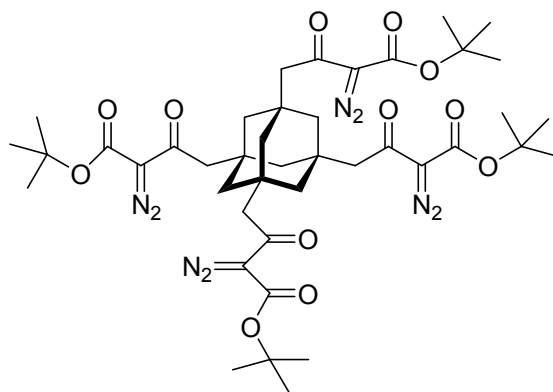
157

β-Keto acid 157. To a solution of *tert*-butyl ester **156** (20 mg, 0.069 mmol) in CH₂Cl₂ (3 mL) at room temperature was added trifluoroacetic acid (0.3 mL). The reaction was stirred at this temperature for 3 h, then the solvent was removed *in vacuo*. The crude material was dried under vacuum for 4 h to afford the β-keto acid **157** (16 mg, 99%) as a white solid: m.p. 118 - 120 °C (CH₂Cl₂); *R_f* 0.39 (hexanes : EtOAc : MeOH, 1 : 1 : 0.2); IR (film) 2906, 2852, 1752, 1702 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.54 (br s, 1H, CO₂H), 3.34 (d, *J* = 13.0 Hz, 1H, CHCO₂H), 2.51 (d, *J* = 13.0 Hz, 1H, CH(CO₂H)CH), 2.17-2.07 (m, 4H, CH₂COCHCO₂H and adamantane), 1.98-1.68 (m, 9H, adamantane), 1.51 (s, 2H, adamantane); ¹³C NMR (100 MHz, CDCl₃) δ 211.4, 174.3, 55.3, 53.1, 51.1, 42.9, 38.2, 37.9, 37.0, 35.8, 29.6, 29.1, 28.5, 27.8; MS (EI) *m/z* 234 (M⁺); HRMS (EI) *m/z* calc for C₁₄H₁₈O₃ 234.1256, found: 234.1254.



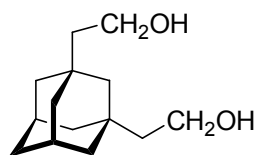
158

Tetra- β -keto ester 158. A solution of tetra-aldehyde **96** (30 mg, 0.099 mmol) in CH_2Cl_2 (3 mL) was added to a stirred mixture of anhydrous SnCl_2 (7.5 mg, 0.040 mmol) and *tert*-butyl diazoacetate (0.060 mL, 0.43 mmol) in CH_2Cl_2 (2 mL) at 0 °C. After 2 h of stirring at room temperature, the mixture was quenched with brine (10 mL) and extracted with CH_2Cl_2 (3 x 15 mL). The organic extracts were dried over MgSO_4 , filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (hexanes : EtOAc, 4 : 1) to afford the tetra- β -keto ester **158** (ca. 4 : 1 all keto : all enol forms) as a colourless oil (61 mg, 81%); R_f 0.41 (hexanes : EtOAc, 2 : 1); IR (film) 2978, 2932, 1738, 1714, 1638 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): (all keto form) δ 3.26 (s, 8H, $\text{CH}_2\text{CO}_2^t\text{Bu}$), 2.33 (s, 8H, $\text{CH}_2\text{COCH}_2\text{CO}_2^t\text{Bu}$), 1.48 (s, 12H, adamantane methylene), 1.45 (s, 36H, $\text{C}(\text{CH}_3)_3$); (enol form) δ 12.19 (s, 4H, $\text{C}(\text{OH})=\text{CHCO}_2^t\text{Bu}$), 4.77 (s, 4H, $\text{C}(\text{OH})=\text{CHCO}_2^t\text{Bu}$), 1.94 (s, 8H, $\text{CH}_2\text{C}(\text{OH})=\text{CHCO}_2^t\text{Bu}$), 1.48 (s, 12H, adamantane methylene), 1.45 (s, 36H, $\text{C}(\text{CH}_3)_3$); ^{13}C NMR (100 MHz, CDCl_3): (keto form) δ 202.0, 166.2, 81.8, 52.6, 48.6, 44.7, 34.7, 28.0; (enol form) δ 174.9, 172.4, 93.1, 81.9, 54.2, 45.2, 34.9, 28.3; MS (ES) m/z 783 ($\text{M}+\text{Na}^+$); HRMS (ES) m/z calc for $\text{C}_{42}\text{H}_{64}\text{O}_{12}\text{Na}$ 783.4295, found: 783.4293; Anal. Calc for $\text{C}_{42}\text{H}_{64}\text{O}_{12}$: C, 66.29; H, 8.48. Found: C, 66.33; H, 8.38.



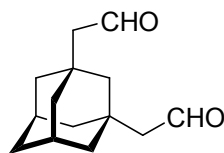
137

Tetra- α -diazo- β -keto ester 137. To a solution of the tetra- β -keto ester **158** (115 mg, 0.151 mmol) and 4-acetamidobenzenesulfonyl azide (160 mg, 0.666 mmol) in dry acetonitrile (10 mL) at 0 °C was added triethylamine (0.255 mL, 1.82 mmol) dropwise. After stirring at room temperature overnight, the reaction mixture was concentrated *in vacuo* and the resultant solid was triturated with diethyl ether/petroleum spirit (1:1) (80 mL). The mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was purified by flash chromatography (hexanes : EtOAc, 4 : 1) to afford tetra-diazo-*tert*-butyl ester **137** (130 mg, 99%) as a viscous oil: R_f 0.57 (hexanes : EtOAc, 2 : 1); IR (film) 2979, 2930, 2130, 1712, 1645, 1310 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 2.67 (s, 8H, $\text{CH}_2\text{C}(\text{O})\text{C}=\text{N}_2$), 1.48 (s, 36H, *tert*-butyl), 1.46 (s, 12H, adamantane methylene); ^{13}C NMR (100 MHz, CDCl_3) δ 191.2, 160.4, 82.9, 78.0, 50.2, 45.2, 35.9, 28.2; MS (ES) m/z 887 ($\text{M}+\text{Na}^+$); HRMS (ES) m/z calc for $\text{C}_{42}\text{H}_{56}\text{N}_8\text{O}_{12}\text{Na}$ 887.3915, found: 887.3923; Anal. Calc for $\text{C}_{42}\text{H}_{56}\text{N}_8\text{O}_{12}$: C, 58.32; H, 6.53; N, 12.96. Found: C, 58.42; H, 6.47; N, 12.86.



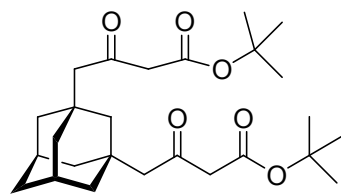
162

1,3-Adamantanediethanol 162.⁶⁸ To a stirred solution of di-acid **161** (1.0 g, 3.97 mmol) in THF (30 mL) at 0 °C was added lithium aluminum hydride (754 mg, 19.8 mmol) in portions. The reaction mixture was then stirred at room temperature for 18 h. A minimal amount of saturated aqueous Na₂SO₄ (1.50 mL) was added carefully to quench the reaction at 0 °C. The mixture was stirred for an additional 30 min, then THF (40 mL) and silica gel (2.0 g) were added. The mixture was filtered through a short pad of Celite, eluting with THF (60 mL). Rotary evaporation and flash chromatography (hexanes : EtOAc : MeOH, 1 : 1 : 0.02 → 1 : 1 : 0.05) gave di-ol **162** as colourless needles (658 mg, 74%): m.p. 112 - 113 °C (MeOH : CH₂Cl₂, 1 : 2) (lit. m.p. 113 - 115 °C); *R*_f 0.39 (hexanes : EtOAc : MeOH, 1 : 1 : 0.02); IR (film) 3389 broad, 2899, 2359, 1644 cm⁻¹; ¹H NMR (400 MHz, DMSO-*d*₆) δ 4.19 (t, *J* = 5.0 Hz, 2H, CH₂OH), 3.45 (td, *J* = 7.6, 5.0 Hz, 4H, CH₂OH), 1.94 (m, 2H, adamantane methine), 1.55 (s, 2H, adamantane methylene), 1.46-1.36 (m, 8H, adamantane methylene and CH₂CH₂OH), 1.28-1.23 (m, 6H, adamantane methylene); ¹³C NMR (100 MHz, DMSO-*d*₆) δ 56.4, 47.9, 46.8, 41.9, 36.3, 32.2, 28.6; MS (EI) *m/z* 224 (M⁺); HRMS (EI) *m/z* calc for C₁₄H₂₄O₂ 224.1776, found: 224.1773. All spectroscopic data were consistent with the literature values.⁶⁸



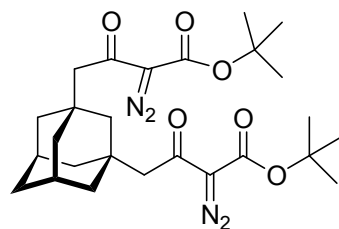
163

1,3-Adamantanediethanal 163. A solution of oxalyl chloride (0.284 mL, 3.30 mmol) in CH_2Cl_2 (2 mL) was cooled to -78°C . Under vigorous stirring, A solution of DMSO (0.47 mL, 6.61 mmol) in CH_2Cl_2 (2 mL) was added over 2 min, and the reaction mixture was stirred at this temperature for an additional 10 min. A solution of di-ol **162** (500 mg, 2.78 mmol) in a mixture of CH_2Cl_2 (4 mL) and anhydrous DMSO (2 mL) was added slowly, and the reaction mixture was stirred at -78°C for 1 h. After this, triethylamine (2.30 mL) was added dropwise, and the mixture was allowed to warm up to room temperature for 1 h. Water (15 mL) was added and the two phases were separated. The organic layer was washed with 5% aqueous HCl (10 mL), water (10 mL), 5% aqueous NaHCO_3 (10 mL) and brine (10 mL), dried over MgSO_4 , filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (hexanes : EtOAc, 8 : 1) to afford the di-aldehyde **163** as a colourless oil (150 mg, 83%): R_f 0.52 (hexanes : EtOAc, 2 : 1); IR (film) 2901, 2848, 1719 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 9.86 (t, $J = 3.1$ Hz, 2H, CH_2CHO), 2.12 (d, $J = 3.1$ Hz, 4H, CH_2CHO), 2.10 (m, 2H, adamantane methine), 1.69-1.58 (m, 12H, adamantane methylene); ^{13}C NMR (100 MHz, CDCl_3) δ 202.9, 56.6, 47.7, 41.7, 35.7, 33.9, 28.6; MS (EI) m/z 220 (M^+); HRMS (EI) m/z calc for $\text{C}_{14}\text{H}_{20}\text{O}_2$ 220.1463, found: 220.1462.



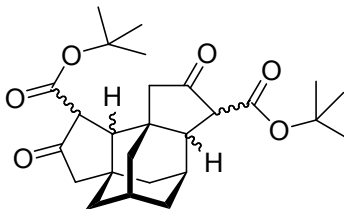
164

Di-β-keto ester 164. A solution of di-aldehyde **163** (148 mg, 0.673 mmol) in CH₂Cl₂ (2 mL) was added to a stirred mixture of anhydrous SnCl₂ (38 mg, 0.202 mmol) and *tert*-butyl diazoacetate (0.24 mL, 1.68 mmol) in CH₂Cl₂ (4 mL). After 1.5 h of stirring at room temperature, the mixture was washed with brine (5 mL) and extracted with CH₂Cl₂ (3 x 10 mL). The organic extracts were dried over MgSO₄, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (hexanes : EtOAc, 12 : 1) to afford the di-β-keto ester **164** (*ca.* 2.5 : 1 all keto : all enol forms) as a viscous colourless oil (225 mg, 75%); *R_f* 0.51 (hexanes : EtOAc, 4 : 1); IR (film) 2903, 1739, 1713, 1638 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): (all keto form) δ 3.30 (s, 4H, CH₂CO₂C(CH₃)₃), 2.29 (s, 4H, CH₂COCH₂CO₂C(CH₃)₃), 2.05 (s, 2H, adamantane methine), 1.64-1.54 (m, 12H, adamantane methylene), 1.47 (s, 18H, CH₂CO₂C(CH₃)₃); (all enol form) δ 12.21 (s, 2H, HOC=CH), 4.80 (s, 2H, HOC=CH), 2.05 (s, 2H, adamantane methine), 1.92 (s, 4H, CH₂C(OH)=CH), 1.64-1.54 (m, 12H, adamantane methylene), 1.50 (s, 9H, CH₂CO₂C(CH₃)₃); ¹³C NMR (100 MHz, CDCl₃): (all keto form) δ 202.6, 166.4, 81.8, 55.3, 53.0, 46.9, 41.3, 34.1, 28.7, 28.0; (all enol form) δ 175.7, 172.6, 92.9, 80.7, 49.5, 47.5, 41.7, 35.8, 28.9, 28.4; MS (ES) *m/z* 471 (M+Na⁺); HRMS (ES) *m/z* calc for C₂₆H₄₀O₆Na 471.2723, found: 471.2715; Anal. Calc for C₂₆H₄₀O₆: C, 69.61; H, 8.99. Found: C, 69.56; H, 9.04.



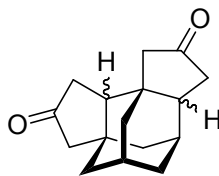
159

Di- α -diazo- β -keto ester 159. To a stirred solution of the di- β -keto ester **164** (210 mg, 0.469 mmol) and 4-acetamidobenzenesulfonyl azide (248 mg, 1.03 mmol) in dry acetonitrile (12 mL) at 0 °C was added triethylamine (0.395 mL, 2.81 mmol) dropwise. After stirring at room temperature for 4 h, the reaction mixture was concentrated *in vacuo* and the resultant solid was triturated with diethyl ether/petroleum spirit (1:1) (80 mL). The mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was purified by flash chromatography (hexanes : EtOAc, 20 : 1) to afford di- α -diazo- β -keto ester **159** (184 mg, 79%) as a viscous colourless oil: R_f 0.60 (hexanes : EtOAc, 4 : 1); IR (film) 2904, 2129, 1712, 1648 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 2.65 (s, 4H, $\text{CH}_2\text{COC}(\text{N}_2)$), 1.97 (m, 2H, adamantane methine), 1.61-1.54 (m, 12H, adamantane methylene), 1.49 (s, 18H, $\text{C}(\text{CH}_3)_3$); ^{13}C NMR (100 MHz, CDCl_3) δ 191.8, 160.5, 83.0, 78.2, 51.0, 47.2, 41.4, 35.9, 35.1, 29.0, 28.3; MS (ES) m/z 471 ($\text{M}+\text{Na}^+$); HRMS (ES) m/z calc for $\text{C}_{26}\text{H}_{40}\text{O}_6\text{Na}$ 471.2723, found: 471.2715.



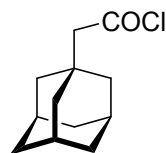
160

Di-β-keto ester 160. Di-rhodium tetra-acetate (17 mg, 0.038 mmol) was added to a stirred solution of di-α-diazo-β-keto ester **159** (126 mg, 0.252 mmol) in CH₂Cl₂ (6 mL) at room temperature. The reaction was stirred at room temperature for 1 h, and the solvent was removed *in vacuo*. The crude product was purified by flash chromatography (hexanes : EtOAc, 10 : 1 → 8 : 1) to afford the insertion product **160** (57 mg, 52%) as a colourless viscous oil: *R_f* 0.25 (hexanes : EtOAc, 4 : 1); IR (film) 2913, 2859, 1753, 1720 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 3.34-3.13 (m, 2H, CHCO₂C(CH₃)₃), 2.77-2.45 (m, 2H, CHCHCO₂C(CH₃)₃), 2.31-1.61 (m, 14H, CH₂C=O and adamantane), 1.48-1.45 (m, 18H, CO₂C(CH₃)₃); See **Appendix 5** for ¹³C NMR; MS (EI) *m/z* 444 (M⁺); HRMS (EI) *m/z* calc for C₂₆H₃₆O₆ 444.2512, found: 444.2514.



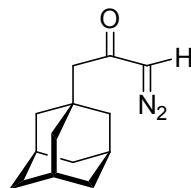
165

Di-cyclopentanone 165. To a stirred solution of di-*tert*-butyl ester **160** (28 mg, 0.063 mmol) in dry chlorobenzene (5 mL) at room temperature was added trifluoroacetic acid (0.5 mL). The reaction was then stirred at 115 °C for 3 h, and the solvent was removed *in vacuo*. The crude product was purified by flash chromatography (hexanes : EtOAc, 4 : 1) to afford the di-ketone **165** (15 mg, 97%) as a colourless oil: R_f 0.24 (hexanes : EtOAc, 2 : 1); IR (film) 2910, 2856, 1740 cm^{-1} ; See **Appendix 6** for ^1H and ^{13}C NMR; MS (EI) m/z 244 (M^+); HRMS (EI) m/z calc for $\text{C}_{16}\text{H}_{20}\text{O}_2$ 244.1463, found: 244.1464; Anal. Calc for $\text{C}_{16}\text{H}_{20}\text{O}_2$: C, 78.65; H, 8.25. Found: C, 78.55; H, 8.37.



138

1-Adamantaneacetic acid chloride 138. To 1-adamantaneacetic acid (**174**) (1.50 g, 7.73 mmol) in a flame-dried flask fitted with a reflux condenser was added freshly distilled thionyl chloride (12 mL). The mixture was refluxed with vigorous stirring for 5 h and the excess thionyl chloride was removed *in vacuo*. Then dry benzene (15 mL) was added which was further removed *in vacuo* to give a light yellow oil. The oil was placed under vacuum overnight to afford 1.65 g (99%) of crude 1-adamantaneacetic acid chloride **138** as a light yellow oil: IR (film) 2904, 2850, 1797, 1451 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 2.70 (s, 2H, CH_2COCl), 1.99 (s, 3H, adamantane methine), 1.74-1.67 (m, 12H, adamantane methylene); ^{13}C NMR (75 MHz, CDCl_3) δ 170.9, 60.7, 41.6, 36.4, 34.0, 28.3.

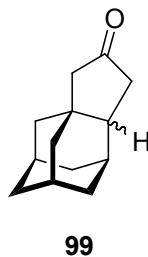


139

1-Diazo-3-(1-adamantyl)-2-propanone 139.⁴³ To a flask was added 50% aqueous KOH (8 mL) and Et₂O (20 mL). The two phase mixture was then cooled to 0 °C, and *N*-nitroso-*N*-methyl urea (**175**) (3.0 g, 28.6 mmol) was added in small portions with stirring. The mixture was stirred for an additional 15 min and the bright yellow organic layer was carefully decanted into a flask and cooled at 0 °C.

A solution of acid chloride **138** (1.5 g, 7.04 mmol) in Et₂O (10 mL) was added dropwise to the above prepared ice-cold CH₂N₂ solution in Et₂O with stirring. The reaction mixture was stirred at 0 °C for 2 h, and then left at room temperature overnight. Removal of solvent *in vacuo* gave diazo-ketone **139** as a yellow oil (1.54 g, quantitative yield): *R_f* 0.42 (hexanes : EtOAc, 4 : 1); IR (film) 2902, 2847, 2099, 1631, 1354 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 5.19 (s, 1H, COCHN₂), 2.05 (s, 2H, CH₂CO), 1.97 (s, 3H, adamantane methine), 1.63 (s, 12H, adamantane methylene); MS (CI, NH₃) *m/z* 219 (M + H⁺); HRMS (CI, NH₃) *m/z* calc for C₁₃H₁₉N₂O (M + H⁺) 219.1497, found: 219.1496.

Adamantanecyclopentane-2-one **99.**⁴³



From diazo-ketone **139**⁴³

A solution of the diazo-ketone **139** (1.55 g, 7.11 mmol) in toluene (40 mL) was added slowly during a period of 5 h *via* syringe pump to refluxing toluene (160 mL) containing CuSO₄ (320 mg, 2.0 mmol). The mixture was then heated under reflux for an additional 2 h. The mixture was cooled down to room temperature and filtered, washed with water (50 mL), 5 M aqueous NaOH (50 mL), again with water (50 mL) and brine (50 mL), dried over MgSO₄. Filtration and evaporation *in vacuo* yielded a thick light brown oil. The residue was purified by flash chromatography (hexanes : EtOAc, 50 : 1) to afford the cyclopentanone **99** as colourless crystals (632 mg, 47% over 3 steps):

From β -keto-ethylester **147**

A solution of β -ketoester **147** (46 mg, 0.176 mmol) and NaCl (20 mg, 0.351 mmol) in DMSO (6 mL) and water (0.095 mL, 5.27 mmol) was stirred at 130 - 140 °C for 1.5 h. The solution was cooled to room temperature, diluted with diethyl ether (50 mL) and washed with water (2 x 15 mL) and brine (15 mL). The organic extracts were dried over MgSO₄, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (hexanes : EtOAc, 25 : 1) to afford adamantanecyclopentanone **99** (30 mg, 90%) as colourless crystals:

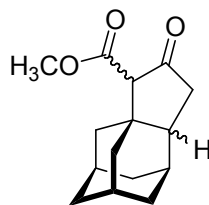
From β -keto-*tert*-butylester **156**

To a stirred solution of *tert*-butyl ester **156** (20 mg, 0.069 mmol) in dry chlorobenzene (5 mL) at room temperature was added trifluoroacetic acid (0.3 mL). The reaction was then stirred at 120 °C for 3 h, and the solvent was removed *in vacuo*. The crude material was dried under vacuum for 3 h to afford the cyclopentanone **99** (13 mg, quantitative yield) as colourless crystals:

From β -keto-acid **157**

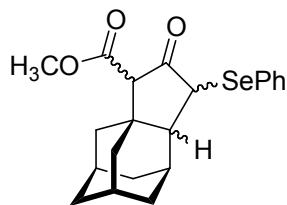
A solution of β -keto-acid **157** (18 mg, 0.077 mmol) in 1,4-dioxane (5 mL) was heated under reflux for 3 h, and the solvent was removed *in vacuo*. The residue was purified by flash chromatography (hexanes : EtOAc, 20 : 1) to afford the cyclopentanone **99** (12 mg, 82%) as colourless crystals:

m.p. 73 - 75 °C (EtOAc) (lit. m.p. 74 - 76 °C); R_f 0.22 (hexanes : EtOAc, 15 : 1); IR (film) 2903, 2851, 1744, 1452 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 2.31(m, 1H, $\text{CH}_2\text{C}=\text{O}$), 2.16 (m, 2H, $\text{CH}_2\text{C}=\text{O}$), 2.07 (m, 1H, $\text{CH}_2\text{C}=\text{O}$), 1.99-1.40 (m, 14H, adamantane methine and methylene); ^{13}C NMR (75 MHz, CDCl_3) δ 219.1, 53.8, 47.3, 43.1, 39.6, 38.6, 37.5, 37.1, 36.9, 29.5, 29.2, 29.1, 27.9; MS (EI) m/z 190 (M^+); HRMS (EI) m/z calc for $\text{C}_{13}\text{H}_{18}\text{O}$ (M^+) 190.1358, found: 190.1358; Anal. Calc for $\text{C}_{13}\text{H}_{18}\text{O}$: C, 82.06; H, 9.53. Found: C, 82.14; H, 9.63.



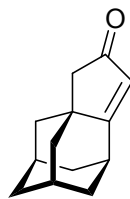
181

β -Keto ester 181. To a stirred solution of lithium bis(trimethylsilyl)amide (1.0 M in THF, 1.86 mL, 1.86 mmol) in THF (5 mL) at $-78\text{ }^{\circ}\text{C}$ was added slowly a solution of cyclopentanone **99** (307 mg, 1.62 mmol) in THF (4 mL). After stirring at $-78\text{ }^{\circ}\text{C}$ for 30 min, methyl cyanoformate (147 μL , 1.86 mmol) was added to the mixture. The mixture was stirred at the same temperature for another 30 min, before quenching with H_2O (10 mL). The aqueous layer was extracted with EtOAc (3 x 15 mL), before the combined organic layers were washed with brine (15 mL), dried over MgSO_4 , filtered and concentrated *in vacuo*. Purification of the residue by chromatography (hexanes : EtOAc, 18 : 1) gave the β -keto ester **181** (300 mg, 75%) as a light yellow oil and a 1 : 1 mixture of diastereomers **181a** and **181b**: R_f 0.42 (hexanes : EtOAc, 4 : 1); IR (film) 2907, 2853, 1757, 1726 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 3.70 (s, **181a**, 3H, CO_2CH_3), 3.67 (s, **181b**, 3H, CO_2CH_3), 2.85 (s, **181a**, 1H, $\text{COCHCO}_2\text{CH}_3$), 2.76 (s, **181b**, 1H, $\text{COCHCO}_2\text{CH}_3$), 2.69-1.41 (m, **181a** and **181b**, 32H, adamantane and cyclopentanone); ^{13}C NMR (75 MHz, CDCl_3) δ 213.1 (210.7), 168.8 (168.4), 67.1 (66.2), 51.8 (51.7), 46.6, 44.5 (42.8), 41.9 (41.7), 39.36 (39.34), 39.3 (38.3), 38.51 (38.48), 33.5, 29.6 (29.4), 29.2 (29.1), 29.00 (28.95), 28.4 (27.7); MS (EI) m/z 248 (M^+); HRMS (EI) m/z calc for $\text{C}_{15}\text{H}_{20}\text{O}_3$ (M^+) 248.1412, found: 248.1411.



182

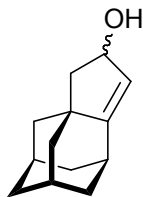
α -Selanyl cyclopentanone 182. A solution of keto-ester **181** (76 mg, 0.306 mmol) in THF (1.5 mL) was added dropwise to a stirred suspension of NaH (60 wt% in mineral oil, 13 mg, 0.32 mmol) in THF (1 mL) at 0 °C. After 30 min of stirring, *n*-BuLi (1.6 M in hexanes, 0.20 mL, 0.322 mmol) was added dropwise and the mixture was stirred for an additional 20 min prior to cooling to -78 °C. PhSeCl (65 mg, 0.337 mmol) in THF (1.5 mL) was added slowly. The mixture was stirred at -78 °C for 0.5 h, before it was quenched with MeOH (2 mL) and saturated aqueous NH₄Cl (2 mL) and allowed to warm up to room temperature. The aqueous layer was extracted with EtOAc (3 x 10 mL), and the combined organic layers were washed with brine (10 mL), dried over MgSO₄, filtered and concentrated *in vacuo*. Purification of the residue by chromatography (hexanes : EtOAc, 25 : 1 $\rightarrow$ 15 : 1) gave the title compound **182** (53 mg, 44%) as a colourless oil along with 32 mg (42%) of recovered starting material **181**. For the product **182**: *R_f* 0.27 (hexanes : EtOAc, 4 : 1); IR (film) 2907, 2854, 1754, 1732 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.50 (d, *J* = 7.0 Hz, 2H, Ar*H*), 7.37 (d, *J* = 6.5 Hz, 1H, Ar*H*), 7.30 (m, 2H, Ar*H*), 3.64 (s, 3H, CO₂CH₃), 2.71 (m, 1H, CHCO₂CH₃), 2.53-2.36 (m, 2H, PhSeCHCH and PhSeCHCH), 2.14-1.39 (m, 13H, adamantane); ¹³C NMR (75 MHz, CDCl₃) δ 202.8, 168.2, 137.7, 129.8, 128.9, 125.2, 68.3, 51.9, 44.8, 42.5, 39.1, 38.2, 37.7, 37.2, 35.2, 29.7, 29.1, 29.0, 27.0; MS (EI) *m/z* 404 (M⁺); HRMS (EI) *m/z* calc for C₂₁H₂₄O₃Se (M⁺) 404.0891, found: 404.0894.



173

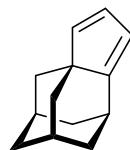
Cyclopentenone 173. To a solution of lithium tetramethylpiperidine (13.1 mmol), prepared from 2,2,6,6-tetramethylpiperidine (2.46 mL, 14.6 mmol) and *n*-BuLi (1.6 M in hexanes, 8.2 mL, 13.1 mmol), in THF (5 mL) cooled to $-78\text{ }^{\circ}\text{C}$ was added dropwise chlorotrimethylsilane (3.74 mL, 29.2 mmol), followed by the dropwise addition of a solution of cyclopentanone **99** (554 mg, 2.92 mmol) in THF (6 mL). After the reaction mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for 20 min, triethylamine (6.3 mL) was added, and the reaction was allowed to warm to room temperature during a period of 1 h. Diethyl ether (50 mL) was added, and the organic solution was washed with water (20 mL) and brine (20 mL), dried over MgSO_4 , and concentrated *in vacuo*. The remaining tetramethylpiperidine was removed under vacuum.

Then $\text{Pd}(\text{OAc})_2$ (643 mg, 2.86 mmol) was added to the above crude mixture of silyl enol ether in dry acetonitrile (10 mL). After the mixture was stirred overnight at room temperature, the mixture was filtered through a short pad of Celite, eluting with diethyl ether. The organic solution was washed with saturated aqueous NH_4Cl (10 mL), dried over MgSO_4 , filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (hexanes : EtOAc, 15 : 1 $\rightarrow$ 10 : 1) to afford the cyclopentenone **173** as a colourless oil (125 mg, 23%) along with recovered starting material **99** (178 mg, 32%). For the title compound **173**: R_f 0.29 (hexanes : EtOAc, 4 : 1); IR (film) 2917, 2851, 1703, 1626 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 5.73 (s, 1H, $\text{COCH}=\text{C}$), 3.06 (s, 2H, CH_2CO), 2.10-2.01 (m, 7H, adamantane methine and methylene), 1.84-1.82 (m, 4H, adamantane methylene), 1.66 (m, 2H, adamantane methylene); ^{13}C NMR (75 MHz, CDCl_3) δ 208.5, 192.3, 121.5, 49.4, 45.2, 43.3, 38.2, 35.7, 35.2, 28.7; MS (EI) m/z 188 (M^+); HRMS (EI) m/z calc for $\text{C}_{13}\text{H}_{16}\text{O}$ (M^+) 188.1201, found: 188.1201.



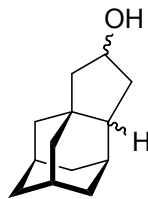
188

Cyclopentenol 188. To a solution of cyclopentenone **173** (55 mg, 0.293 mmol) in dry THF (5 mL) at $-78\text{ }^{\circ}\text{C}$ was added DIBAL-H (1.0 M in hexanes, 0.59 mL, 0.585 mmol) dropwise. After the reaction mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for 30 min, saturated aqueous NH_4Cl (0.16 mL), diethyl ether (10 mL), and silica gel (200 mg) were added. The mixture was allowed to stir vigorously and warm to room temperature. The mixture was filtered through a short pad of anhydrous MgSO_4 , washing with EtOAc. Rotary evaporation and chromatography (hexanes : EtOAc, 8 : 1) gave the cyclopentenol **188** (50 mg, 90%) as a colourless oil: R_f 0.28 (hexanes : EtOAc, 4 : 1); IR (film) 3331 broad, 2902, 2847, 1666 cm^{-1} ; ^1H NMR (400 MHz, C_6D_6) δ 5.25 (d, $J = 2.0$ Hz, 1H, $\text{CH}=\text{C}$), 4.83 (ddd, $J = 7.8, 3.9, 2.0$ Hz, 1H, CHOH), 2.61 (m, 1H, CH_2CHOH), 2.31 (m, 1H, CH_2CHOH), 1.91 (dd, $J = 14.1, 7.8$ Hz, 1H, $\text{CH}=\text{CCH}$), 1.86-1.37 (m, 12H, adamantane); ^{13}C NMR (100 MHz, C_6D_6) δ 157.4, 118.0, 76.3, 48.4, 46.9, 46.3, 46.2, 38.7, 36.7, 33.9, 30.2, 30.0, 29.8; Unable to obtain MS data.



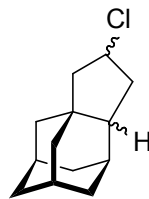
98

Cyclopentadiene 98. Allylic alcohol **188** (48 mg, 0.253 mmol) was dissolved in CDCl_3 (2 mL). After 2 h, CDCl_3 was carefully removed *in vacuo*. The residue was purified by flash chromatography (hexanes only) to afford adamantanocyclopentadiene **98** as a colourless and volatile oil (40 mg, 89%); R_f 0.76 (hexanes : EtOAc, 15 : 1); IR (film) 2914, 2848 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 6.41 (d, $J = 5.0$ Hz, 1H, $\text{CH}=\text{CHCH}=\text{C}$), 6.30 (d, $J = 5.0$ Hz, 1H, $\text{CH}=\text{CHCH}=\text{C}$), 5.82 (s, 1H, $\text{CH}=\text{CHCH}=\text{C}$), 3.06 (apparent s, 1H, $\text{CH}=\text{CHCH}=\text{CCH}$), 2.15 (apparent d, $J = 12.0$ Hz, 2H, adamantane), 2.01 (apparent s, 2H, adamantane), 1.93 (apparent d, $J = 12.0$ Hz, 2H, adamantane), 1.78 (apparent s, 2H, adamantane), 1.51 (apparent d, $J = 11.5$ Hz, 2H, adamantane), 1.12 (apparent d, $J = 11.5$ Hz, 2H, adamantane); ^{13}C NMR (75 MHz, CDCl_3) δ 160.6, 142.7, 130.0, 113.8, 53.0, 41.2, 39.3, 36.1, 33.8, 28.1; MS (EI) m/z 172 (M^+); HRMS (EI) m/z calc for $\text{C}_{13}\text{H}_{16}$ (M^+) 172.1252, found: 172.1253.



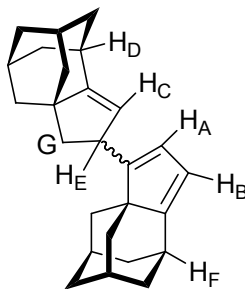
191

Cyclopentanol 191. NaBH₄ (12 mg, 0.316 mmol) was added in one portion to a stirred solution of adamantanecyclopentanone **99** (60 mg, 0.316 mmol) in MeOH (2 mL) at 0 °C. After the reaction mixture was stirred at 0 °C for 1 h, saturated aqueous NH₄Cl (4 mL) was added and the MeOH was removed *in vacuo*. The residue was dissolved in water (20 mL) and extracted with EtOAc (3 x 20 mL). The combined organic solution was washed with brine (20 mL), dried over MgSO₄, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (hexanes : EtOAc, 12 : 1) to afford the alcohol **191** as colourless crystals (48 mg, 80%): m.p. 81 - 83 °C (hexanes : EtOAc, 1 : 2); *R_f* 0.28 (hexanes : EtOAc, 4 : 1); IR (film) 3305 broad, 2904, 2848 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 4.46-4.40 (m, 1H, CHOH), 2.14-1.53 (m, 16H, adamantane and cyclopentane), 1.38-1.30 (m, 3H, adamantane); ¹³C NMR (75 MHz, CDCl₃) δ 72.3, 50.1, 49.7, 44.1, 39.1, 38.9, 38.2, 38.0, 37.7, 30.4, 29.9, 29.6, 28.9; MS (EI) *m/z* 192 (M⁺); HRMS (EI) *m/z* calc for C₁₃H₂₀O (M⁺) 192.1514, found: 192.1518; Anal. Calc for C₁₃H₂₀O: C, 81.20; H, 10.48. Found: C, 81.32; H, 10.38.



192

Chloro-cyclopentane 192. Phosphoryl chloride (POCl_3) (52 μL , 0.56 mmol) was added dropwise to a solution of cyclopentanol **191** (54 mg, 0.280 mmol) in dry pyridine (1.5 mL) at 0 °C. After the reaction mixture was stirred at 0 °C for 4 h, saturated aqueous NH_4Cl (4 mL) was added. The aqueous layer was extracted with diethyl ether (3 x 10 mL) and the combined organic layers were washed with brine (10 mL), dried over MgSO_4 , filtered and concentrated *in vacuo*. Purification of the residue by chromatography (hexanes : EtOAc, 40 : 1) gave the chloride **192** as a colourless oil (36 mg, 74%): R_f 0.74 (hexanes : EtOAc, 15 : 1); IR (film) 2906, 2850, 1452 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 4.47-4.40 (m, 1H, CHCl), 2.43-2.32 (m, 1H, adamantane), 2.13-1.81 (m, 8H, cyclopentane and adamantane), 1.70-1.46 (m, 8H, adamantane), 1.28-1.24 (m, 1H, adamantane); ^{13}C NMR (75 MHz, CDCl_3) δ 57.9, 51.7, 48.1, 43.7, 40.9, 38.8, 38.6, 37.6, 37.3, 30.1, 29.4, 29.3, 28.4; MS (EI) m/z 210 (M^+); HRMS (EI) m/z calc for $\text{C}_{13}\text{H}_{19}\text{Cl}$ (M^+) 210.1175, found: 210.1182; Anal. Calc for $\text{C}_{13}\text{H}_{19}\text{Cl}$: C, 74.09; H, 9.09. Found: C, 73.98; H, 8.97.



201

Triene 201. To a stirring solution of adamantanocyclopentadiene **98** (120 mg, 0.698 mmol) in CH_2Cl_2 (3.5 mL) at 0 °C was added tris(*p*-bromophenyl)-aminium hexachloroantimonate (**199**) (57 mg, 0.070 mmol). The mixture was stirred at 0 °C for 2.5 h. Any remaining cation radicals and cationic species were quenched with methoxide/methanol/ solution and then pouring the mixture into a separatory funnel with the addition of excess CH_2Cl_2 . The crude organic solution was washed with water (3 x 10 mL) to remove inorganic salts and once with brine (10 mL). The organic phase was then dried over MgSO_4 , filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (hexanes only) to afford the adamantanocyclopentadiene dimer **201** (48 mg, 40%) as a colourless oil: R_f 0.78 (hexanes : EtOAc, 15 : 1); IR (film) 2904, 2846, 1445 cm^{-1} ; UV-Vis (hexanes) λ_{max} (log ϵ) 262 (3.76) nm; ^1H NMR (500 MHz, C_6D_6) δ 6.30 (m, 1H, H_A), 5.93 (d, J = 1.9 Hz, 1H, H_B), 5.21 (d, J = 2.0 Hz, 1H, H_C), 3.72 (m, 1H, H_E), 2.98 (m, 1H, H_F), 2.75 (m, 1H, H_D), 2.10-1.20 (m, 26H, adamantane and H_G); ^{13}C NMR (125 MHz, C_6D_6) δ 162.2, 157.9, 153.0, 123.9, 117.4, 114.6, 53.3, 47.3, 47.1, 46.4, 45.9, 41.9, 41.5, 41.4, 40.4, 39.8, 39.5, 38.7, 37.0, 36.5, 34.2, 34.1, 30.39, 30.36, 28.74, 28.70; MS (EI) m/z 344 (M^+); HRMS (EI) m/z calc for $\text{C}_{26}\text{H}_{32}$ (M^+) 344.2504, found: 344.2503.

4. Appendix

Appendix 1: X-ray Crystal Data and Structure Refinement for Compound 91

Identification code	AB0512
Empirical formula	C ₂₂ H ₃₂ O ₄
Formula weight	360.48
Temperature	173(2) K
Diffractometer, wavelength	OD Xcalibur PX Ultra, 1.54248 Å
Crystal system, space group	Monoclinic, P2(1)
Unit cell dimensions	a = 7.2942(7) Å $\alpha = 90^\circ$ b = 11.5286(12) Å $\beta = 92.841(8)^\circ$ c = 11.5044(10) Å $\gamma = 90^\circ$
Volume, Z	966.24(16) Å ³ , 2
Density (calculated)	1.239 Mg/m ³
Absorption coefficient	0.665 mm ⁻¹
F(000)	392
Crystal colour / morphology	Colourless needles
Crystal size	0.23 x 0.07 x 0.05 mm ³
θ range for data collection	3.85 to 70.87°
Index ranges	-8<= <i>h</i> <=8, -13<= <i>k</i> <=13, -13<= <i>l</i> <=13
Reflns collected / unique	8877 / 3459 [R(int) = 0.0378]
Reflns observed [F>4 σ (F)]	2904
Absorption correction	Numeric analytical
Max. and min. transmission	0.96889 and 0.88006
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	3459 / 5 / 252
Goodness-of-fit on F ²	0.984
Final R indices [F>4 σ (F)]	R1 = 0.0330, wR2 = 0.0768
R indices (all data)	R1 = 0.0395, wR2 = 0.0797
Absolute structure parameter	0.07(19)
Extinction coefficient	0.0035(6)
Largest diff. peak, hole	0.183, -0.143 eÅ ⁻³
Mean and maximum shift/error	0.000 and 0.000

Bond Lengths [Å] and Angles [°] for Compound 91

C(1)–C(11)	1.515(2)
C(1)–C(2)	1.542(2)
C(1)–C(6)	1.544(2)
C(1)–C(7)	1.548(2)
C(2)–C(3)	1.535(2)
C(3)–C(15)	1.525(2)
C(3)–C(4)	1.537(2)
C(3)–C(10)	1.549(2)
C(4)–C(5)	1.548(2)
C(5)–C(19)	1.515(2)
C(5)–C(6)	1.537(2)
C(5)–C(9)	1.538(2)
C(7)–C(8)	1.544(2)
C(8)–C(23)	1.523(2)
C(8)–C(10)	1.538(2)
C(8)–C(9)	1.540(2)
C(11)–C(12)	1.328(2)
C(12)–C(13)	1.493(3)
C(13)–O(14)	1.433(2)
C(15)–C(16)	1.339(3)
C(16)–C(17)	1.485(3)
C(17)–O(18)	1.434(2)
C(19)–C(20)	1.327(3)
C(20)–C(21)	1.500(3)
C(21)–O(22)	1.431(2)
C(23)–C(24)	1.328(3)
C(24)–C(25)	1.498(3)
C(25)–O(26)	1.429(2)

C(11)–C(1)–C(2)	107.82(13)
C(11)–C(1)–C(6)	111.72(14)
C(2)–C(1)–C(6)	107.46(13)
C(11)–C(1)–C(7)	112.93(14)
C(2)–C(1)–C(7)	108.12(13)
C(6)–C(1)–C(7)	108.59(13)
C(3)–C(2)–C(1)	112.30(13)
C(15)–C(3)–C(2)	111.39(13)
C(15)–C(3)–C(4)	112.34(14)
C(2)–C(3)–C(4)	109.36(13)
C(15)–C(3)–C(10)	107.58(14)
C(2)–C(3)–C(10)	107.58(13)
C(4)–C(3)–C(10)	108.42(13)
C(3)–C(4)–C(5)	111.04(13)
C(19)–C(5)–C(6)	108.02(14)
C(19)–C(5)–C(9)	113.85(14)
C(6)–C(5)–C(9)	108.13(13)
C(19)–C(5)–C(4)	110.23(13)
C(6)–C(5)–C(4)	108.22(13)
C(9)–C(5)–C(4)	108.23(14)
C(5)–C(6)–C(1)	112.59(13)
C(8)–C(7)–C(1)	110.89(13)
C(23)–C(8)–C(10)	113.84(14)
C(23)–C(8)–C(9)	107.89(13)
C(10)–C(8)–C(9)	107.91(14)
C(23)–C(8)–C(7)	109.32(14)
C(10)–C(8)–C(7)	108.84(14)
C(9)–C(8)–C(7)	108.94(13)
C(5)–C(9)–C(8)	112.04(13)
C(8)–C(10)–C(3)	111.54(14)
C(12)–C(11)–C(1)	131.15(16)

C(11)–C(12)–C(13)	129.38(18)
O(14)–C(13)–C(12)	112.03(15)
C(16)–C(15)–C(3)	130.24(17)
C(15)–C(16)–C(17)	129.66(17)
O(18)–C(17)–C(16)	112.42(15)
C(20)–C(19)–C(5)	131.88(17)
C(19)–C(20)–C(21)	129.29(18)
O(22)–C(21)–C(20)	111.65(16)
C(24)–C(23)–C(8)	131.15(17)
C(23)–C(24)–C(25)	130.31(17)
O(26)–C(25)–C(24)	112.17(16)

Appendix 2: X-ray Crystal Data and Structure Refinement for Compound 90

Identification code	AB0533
Empirical formula	C ₂₆ H ₄₀ O ₄
Formula weight	416.58
Temperature	173(2) K
Diffractometer, wavelength	OD Xcalibur 3, 0.71073 Å
Crystal system, space group	Monoclinic, C2
Unit cell dimensions	a = 22.4705(19) Å $\alpha = 90^\circ$ b = 10.5816(10) Å $\beta = 96.483(9)^\circ$ c = 9.5532(12) Å $\gamma = 90^\circ$
Volume, Z	2257.0(4) Å ³ , 4
Density (calculated)	1.226 Mg/m ³
Absorption coefficient	0.080 mm ⁻¹
F(000)	912
Crystal colour / morphology	Colourless plates
Crystal size	0.19 x 0.10 x 0.05 mm ³
θ range for data collection	4.44 to 32.70°
Index ranges	-33 ≤ h ≤ 33, -15 ≤ k ≤ 15, -11 ≤ l ≤ 13
Reflns collected / unique	11690 / 6144 [R(int) = 0.1577]
Reflns observed [F > 4σ(F)]	2993
Absorption correction	Numeric analytical
Max. and min. transmission	0.99590 and 0.98684
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	6144 / 15 / 293
Goodness-of-fit on F ²	1.001
Final R indices [F > 4σ(F)]	R ₁ = 0.0996, wR ₂ = 0.2330 R ₁ ⁺ = 0.0996, wR ₂ ⁺ = 0.2330 R ₁ ⁻ = 0.0997, wR ₂ ⁻ = 0.2330
R indices (all data)	R ₁ = 0.1659, wR ₂ = 0.2818
Absolute structure parameter	x = 0(3), x ⁻ = 9(3) Absolute structure indeterminate
Largest diff. peak, hole	0.320, -0.270 eÅ ⁻³
Mean and maximum shift/error	0.000 and 0.001

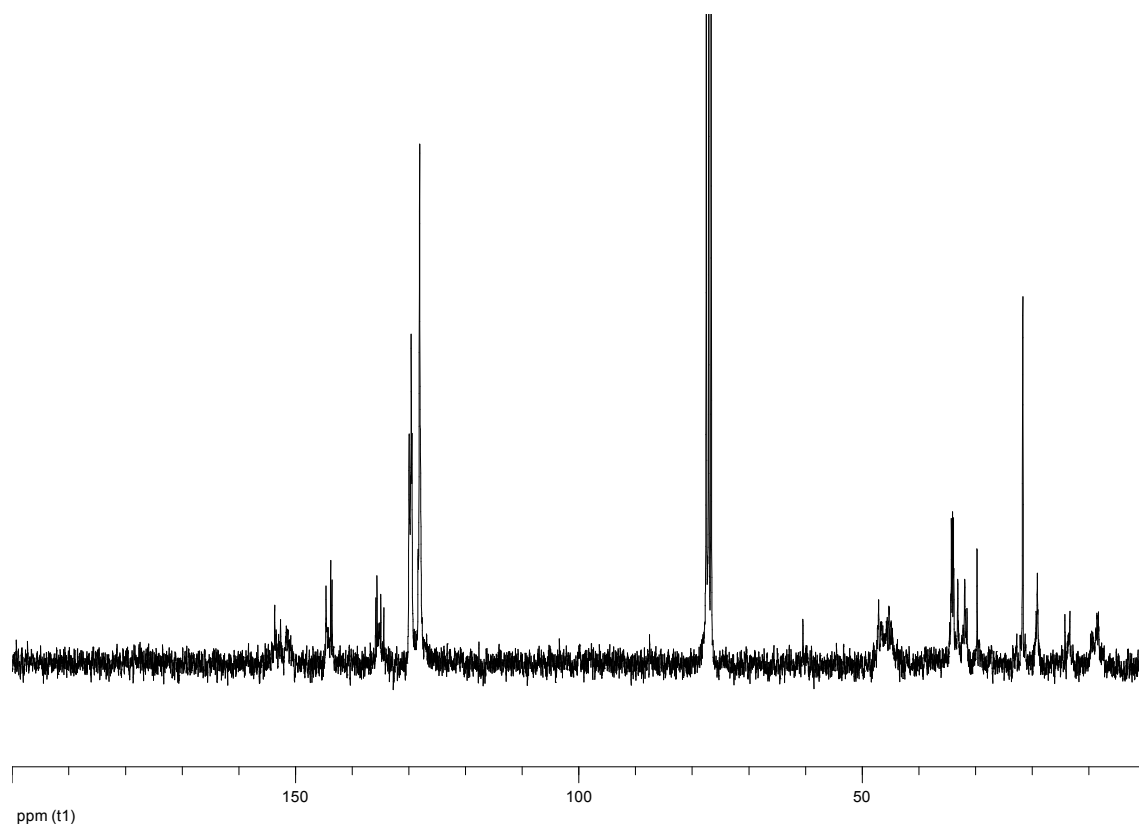
Bond Lengths [Å] and Angles [°] for Compound 90

C(1)–C(11)	1.524(5)
C(1)–C(3)	1.541(5)
C(1)–C(4)	1.543(5)
C(1)–C(2)	1.550(5)
C(2)–C(5)	1.531(5)
C(3)–C(7)	1.543(5)
C(4)–C(9)	1.531(5)
C(5)–C(6)	1.532(5)
C(5)–C(16)	1.544(6)
C(5)–C(10)	1.552(5)
C(6)–C(7)	1.532(5)
C(7)–C(21)	1.527(5)
C(7)–C(8)	1.544(5)
C(8)–C(9)	1.517(5)
C(9)–C(26)	1.530(5)
C(9)–C(10)	1.536(6)
C(11)–C(12)	1.500(7)
C(11)–C(13)	1.506(6)
C(12)–C(13)	1.513(7)
C(13)–C(14)	1.499(7)
C(14)–O(15)	1.443(5)
C(16)–C(17)	1.485(7)
C(16)–C(18)	1.506(6)
C(17)–C(18)	1.506(7)
C(18)–C(19)	1.468(8)
C(19)–O(20)	1.430(8)
C(21)–C(22)	1.488(7)
C(21)–C(23)	1.502(6)
C(22)–C(23)	1.479(7)
C(23)–C(24)	1.518(7)
C(24)–O(25)	1.420(6)
C(26)–C(28')	1.373(16)
C(26)–C(28)	1.456(7)
C(26)–C(27)	1.600(9)
C(26)–C(27')	1.67(2)
C(27)–C(28)	1.496(11)
C(28)–C(29)	1.488(10)
C(29)–O(30)	1.457(9)
C(27')–C(28')	1.514(19)
C(28')–C(29')	1.483(15)
C(29')–O(30')	1.457(12)

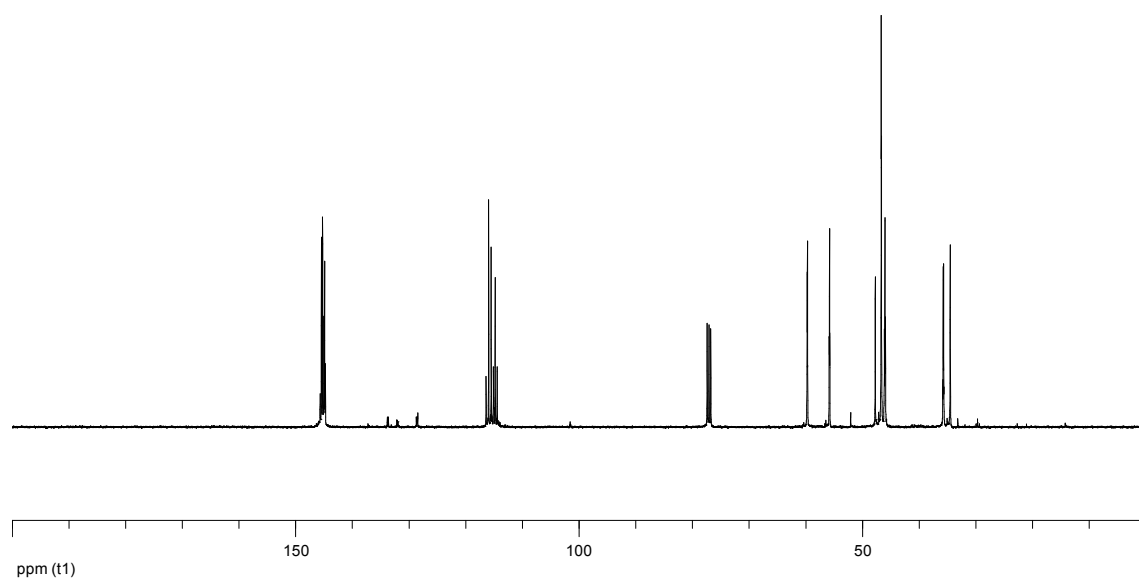
C(11)–C(1)–C(3)	114.6(3)
C(11)–C(1)–C(4)	107.8(3)
C(3)–C(1)–C(4)	107.1(3)
C(11)–C(1)–C(2)	109.6(3)
C(3)–C(1)–C(2)	109.2(3)
C(4)–C(1)–C(2)	108.3(3)
C(5)–C(2)–C(1)	111.4(3)
C(1)–C(3)–C(7)	111.2(3)
C(9)–C(4)–C(1)	112.2(3)
C(2)–C(5)–C(6)	109.1(3)
C(2)–C(5)–C(16)	114.3(3)
C(6)–C(5)–C(16)	110.5(3)
C(2)–C(5)–C(10)	107.8(3)
C(6)–C(5)–C(10)	108.6(3)
C(16)–C(5)–C(10)	106.4(3)
C(7)–C(6)–C(5)	111.4(3)
C(21)–C(7)–C(6)	115.4(3)
C(21)–C(7)–C(3)	109.3(3)

C(6)-C(7)-C(3)	109.8(3)
C(21)-C(7)-C(8)	106.9(3)
C(6)-C(7)-C(8)	107.7(3)
C(3)-C(7)-C(8)	107.4(3)
C(9)-C(8)-C(7)	112.8(3)
C(8)-C(9)-C(26)	107.6(3)
C(8)-C(9)-C(4)	108.3(3)
C(26)-C(9)-C(4)	115.7(3)
C(8)-C(9)-C(10)	107.8(3)
C(26)-C(9)-C(10)	109.0(3)
C(4)-C(9)-C(10)	108.1(3)
C(9)-C(10)-C(5)	111.7(3)
C(12)-C(11)-C(13)	60.4(3)
C(12)-C(11)-C(1)	126.0(4)
C(13)-C(11)-C(1)	127.8(3)
C(11)-C(12)-C(13)	60.0(3)
C(14)-C(13)-C(11)	125.0(4)
C(14)-C(13)-C(12)	120.7(4)
C(11)-C(13)-C(12)	59.6(3)
O(15)-C(14)-C(13)	109.9(4)
C(17)-C(16)-C(18)	60.4(3)
C(17)-C(16)-C(5)	124.8(4)
C(18)-C(16)-C(5)	129.5(4)
C(16)-C(17)-C(18)	60.5(3)
C(19)-C(18)-C(17)	121.8(5)
C(19)-C(18)-C(16)	127.8(4)
C(17)-C(18)-C(16)	59.1(3)
O(20)-C(19)-C(18)	111.4(6)
C(22)-C(21)-C(23)	59.3(3)
C(22)-C(21)-C(7)	126.0(4)
C(23)-C(21)-C(7)	129.5(4)
C(23)-C(22)-C(21)	60.8(3)
C(22)-C(23)-C(21)	59.9(3)
C(22)-C(23)-C(24)	119.3(4)
C(21)-C(23)-C(24)	125.9(4)
O(25)-C(24)-C(23)	112.1(4)
C(28')-C(26)-C(28)	33.7(8)
C(28')-C(26)-C(9)	135.8(8)
C(28)-C(26)-C(9)	134.1(5)
C(28')-C(26)-C(27)	24.7(7)
C(28)-C(26)-C(27)	58.4(5)
C(9)-C(26)-C(27)	123.3(5)
C(28')-C(26)-C(27')	58.6(8)
C(28)-C(26)-C(27')	25.6(6)
C(9)-C(26)-C(27')	116.0(8)
C(27)-C(26)-C(27')	82.7(7)
C(28)-C(27)-C(26)	56.0(4)
C(26)-C(28)-C(29)	124.4(6)
C(26)-C(28)-C(27)	65.6(5)
C(29)-C(28)-C(27)	119.0(8)
O(30)-C(29)-C(28)	107.5(6)
C(28')-C(27')-C(26)	50.7(9)
C(26)-C(28')-C(29')	124.8(14)
C(26)-C(28')-C(27')	70.7(11)
C(29')-C(28')-C(27')	116.0(14)
O(30')-C(29')-C(28')	109.8(11)

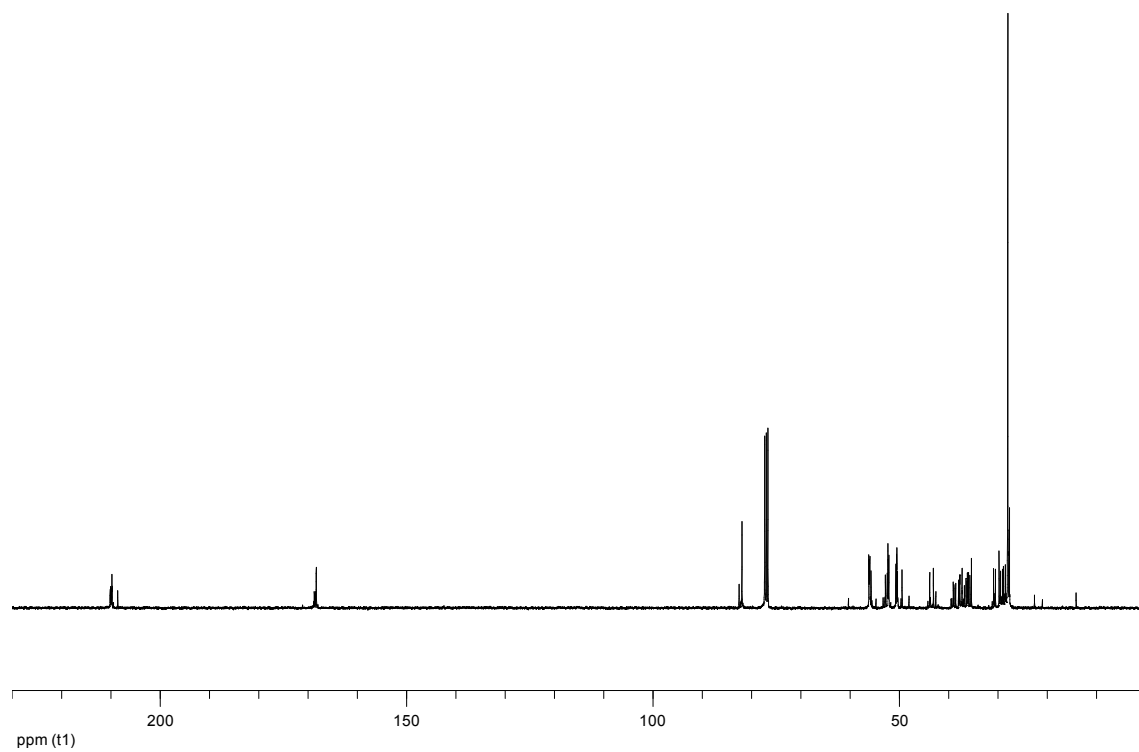
Appendix 3: ^{13}C NMR of Compound 89 in CDCl_3 (75 MHz)



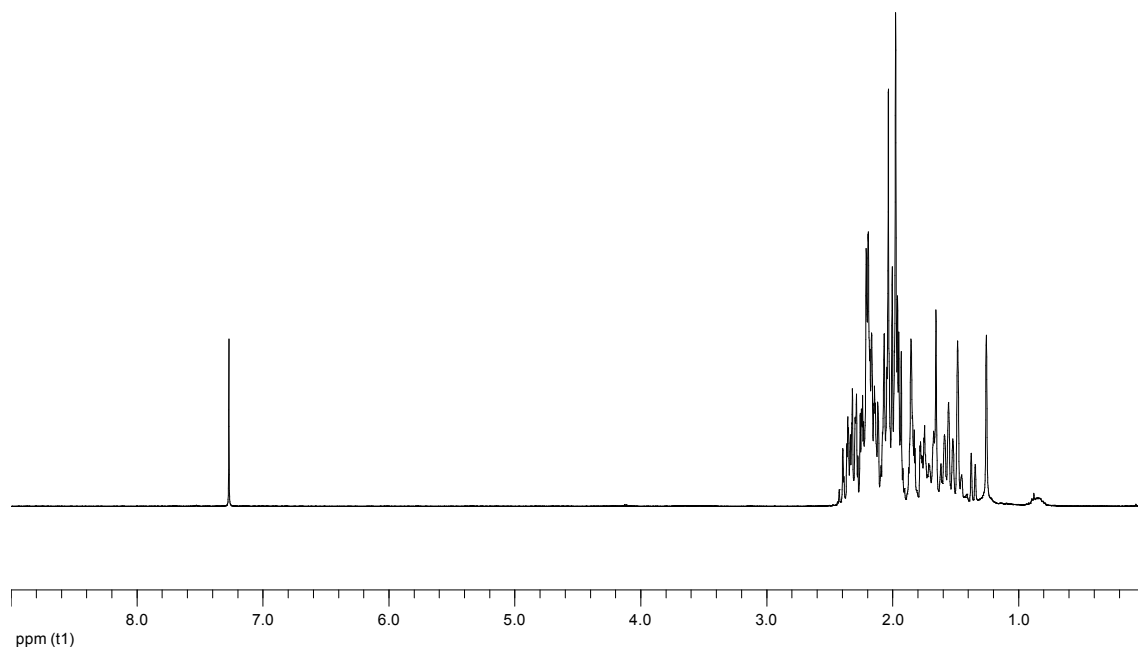
Appendix 4: ^{13}C NMR of Compound 140 in CDCl_3 (100 MHz)



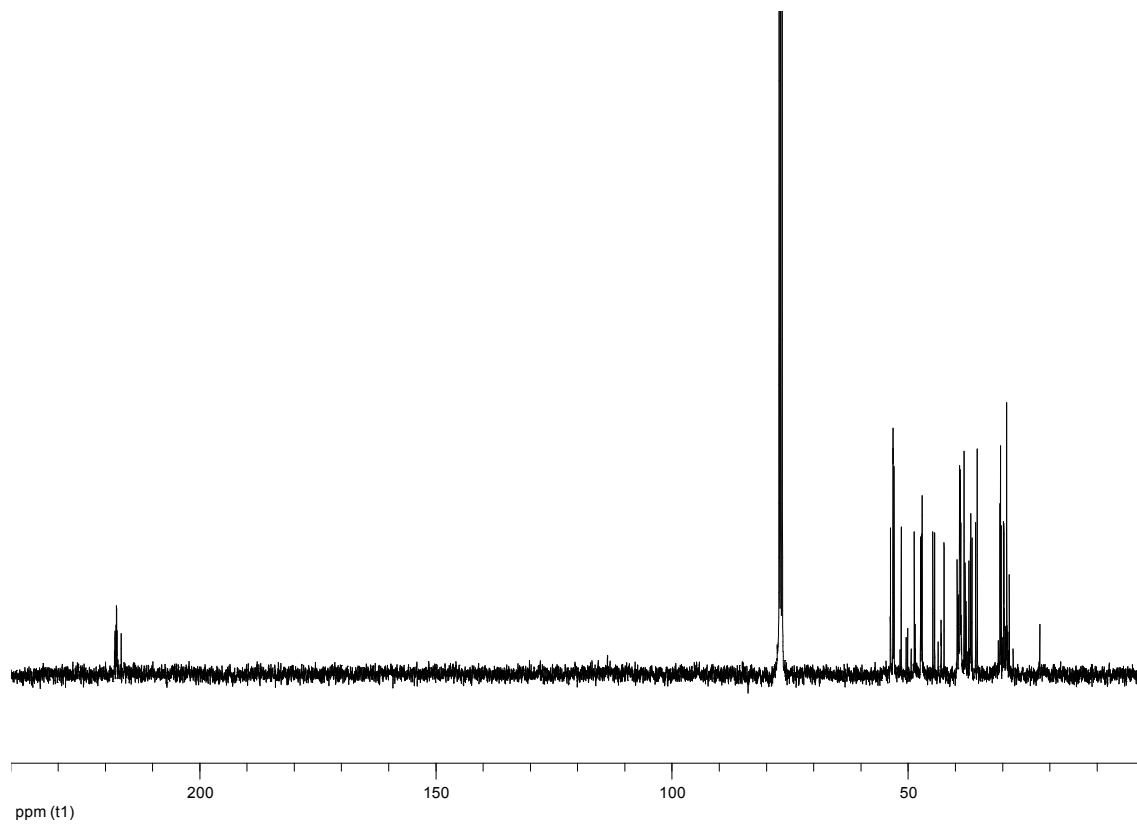
Appendix 5: ^{13}C NMR of Compound 160 in CDCl_3 (100 MHz)



Appendix 6: ^1H NMR of Compound 165 in CDCl_3 (400 MHz)



^{13}C NMR of Compound 165 in CDCl_3 (100 MHz)



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